103

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Y 4.SM 1:103-2

Pricing of Drugs Codeveloped by Fed...

HEARING

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND TECHNOLOGY

OF THE

COMMITTEE ON SMALL BUSINESS
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

FIRST SESSION

WASHINGTON, DC, JANUARY 25, 1993

Printed for the use of the Committee on Small Business

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PRICING OF DRUGS CODEVELOPED BY FEDERAL LABORATORIES AND PRIVATE COMPANIES

MONDAY, JANUARY 25, 1993

House of Representatives,
Subcommittee on Regulation, Business
Opportunities, and Technology,
Committee on Small Business,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:50 a.m., in room 2226, Rayburn House Office Building, Hon. Ron Wyden (chairman of the subcommittee) presiding.

Chairman Wyden. The subcommittee will come to order.

Today, the Subcommittee on Regulation and Business Opportunities continues its inquiry into the pricing of drugs developed with significant governmental support. This subject has been a subcommittee priority because as drug prices continue to skyrocket, a growing percentage of medicines are brought to the marketplace with the taxpayers having funded much of the research through Federal research laboratory support and corporate investment tax credits.

In fact, up to half of the most valuable cancer and AIDS drugs are developed with substantial taxpayer support. In addition, through the Orphan Drug Act, the Government supports the research and development of drugs such as Ceredase, which treats a fatal immune disorder. The subcommittee will hear today that this drug is so expensive that many middle-income Americans simply cannot afford to buy it.

The subcommittee and the witnesses appearing today will be discussing a number of drugs. The subcommittee intends to use Taxol, described by the National Cancer Institute as the most promising anticancer drug in the last 15 years, as a special case study.

Residents of the Pacific Northwest are especially interested in this issue because currently the primary source of Taxol is from the bark of the Pacific yew tree, a species native to the forests of Oregon and Washington.

The policy questions in front of the subcommittee are emblematic of the crises facing the Nation. Americans want new cures for dread diseases on the market as quickly as possible.

Americans feel just as strongly that those cures must be affordable. Last year, Americans spent $59 billion on drugs. Much of that therapy came from the seven major U.S. pharmaceutical companies, companies which enjoyed immense profit increases during the decade of the 1980's.

The Federal Government, in attempting to respond to concerns that new drugs be made available, and quickly, at affordable prices, has developed a significant technology transfer program utilizing cooperative research and development agreements known as CRADA's that allow Government laboratory discoveries to be made available to private drug companies.

This cooperative process between Government and private enterprise should be encouraged because it can bring promising drugs to ailing citizens more quickly than would otherwise be the case. At the same time, drug companies must not be allowed to exploit the taxpayer by charging prices that are unreasonable. The challenge for the Federal Government is to develop a policy so that our citizens don't have to choose between getting sick or going broke.

In the instance of Taxol, there are a number of facts that are not in dispute: In a September 10, 1991, letter to the Chair of this subcommittee, Dr. Samuel Broder, director of the National Cancer Institute, wrote, and I quote, "Taxol was discovered and developed within the National Cancer Institute's comprehensive anticancer drug development program."

In the same letter, Dr. Broder said that the National Cancer Institute was responsible for, and I quote, "One, the initial collection and recollection of bark; two, all biological screening in both cell culture and animal tumor systems; three, chemical purification, isolation and structure identification; four, large-scale production, from collection of bark through preparation of material suitable for human use; five, the development and production of a suitable intravenous dosage formulation; six, preclinical toxicology; seven, the filing of an Investigational New Drug Application [INDA] with the FDA, along with the required documentation; and eight, sponsorship of all activities, including efforts directed toward total and partial synthesis of the drug, have been supported through NCI research grants and intramural programs." The collective cost of this Federal assistance was $32 million at the end of fiscal year 1992.

The Federal Government has also said that all "new and raw data from federally funded research would be made available exclusively to Bristol-Myers Squibb" when the company is "engaged in the commercial development and marketing of Taxol."

In addition, the Bush administration gave Bristol-Myers Squibb virtually exclusive access to Pacific yews on the Federal forestland. Beyond a small management fee, the company pays virtually nothing for this only approved source of medicinal Taxol.

In a December 3, 1992, letter to the Chair inquiring as to whether Bristol-Myers Squibb has provided any pricing analysis for Taxol to the Federal Government, the National Institutes of Health responded, and I quote, "Bristol-Myers Squibb has indicated it will not provide detailed information about its costs to the National Institutes of Health."

Because Bristol-Myers Squibb will divulge nothing about the elements used in establishing the price of Taxol, taxpayers must assume that an arbitrary price has been established by determining that Bristol-Myers Squibb may charge a price similar to a range of other arbitrarily priced drugs.

The production price paid by the National Cancer Institute for experimental quantities of refined Taxol ranged between 60 cents and 90 cents per milligram. Bristol-Myers Squibb has announced it would price the drug at $986 per 3-week treatment cycle or about $4.87 per milligram, a markup of six to eight times NCI's production costs prior to the agreement.

Wall Street analysts have said that Taxol will achieve worldwide sales of up to $800 million per year, and there is no legal restraint on the right of Bristol-Myers Squibb to patent Taxol analogues or synthetic substitutes.

These basic facts call into question the foundations of the public/private drug development partnership. As long as Bristol-Myers keeps secret and confidential all matters related to its developmental cost, who could know if the price is justified?

Given the Government's role in developing these drugs, our citizens believe Congress should do more than accept a "trust us" argument from the pharmaceutical giants of America.

In the instance of Taxol, because Bristol-Myers decided that its Federal partner and investor doesn't need to know how it arrived at its price, Congress is left with another question: Were Bristol-Myers' development efforts aimed at discovering or purchasing a synthetic, and patentable, alternative to bark-produced Taxol to solidify the company's competitive position in the anticancer drug market?

Again, the taxpayer and the consumer are in the dark. Bristol-Myers and other companies claim that if the Government insists on answers to basic questions about pricing, they will walk away from the table and Americans will die as a result. They have in effect said "Do it our way, or no way," betting on the prospect that our desire for new cures is so great that no one will insist on data justifying the taxpayer expenditures.

Those days are over. American consumers who have funded drug development through the gifts of corporate tax credits and Federal laboratory research should not be bludgeoned by price gouging. There are limits to what Americans ought to pay for drugs developed through billions of dollars of Federal research and Federal tax credits.

Americans should not be held hostage to drug companies who threaten to walk away from cures if the Congress requires reasonable price justification.

What is needed are rules so that Government can assist private companies in getting blockbuster drugs to market quickly, while ensuring our tax dollars are spent wisely and allowing the companies to make a reasonable profit.

To this end, a number of ideas have been advanced:

Before entering into a cooperative venture, the drug price could be negotiated based on a formula that estimates the cost and the profits of the new drug.

The National Institutes of Health could commission an informal panel of experts to assess the price proposed by a company. The panel would work on a confidential basis but with access to proprietary costs and investment data held by the company.

On a more formal basis, the National Institutes of Health or the Department of Health and Human Services could form a permanent secretariat on pricing, including expertise in the appropriate area of analyses. The secretariat would give an affirmative or a negative as to whether the minimum thresholds for fair and reasonable pricing specified in a cooperative research and development agreement had been met.

Paralleling the arrangements that are now used for some defense contractors, agreements could include stipulations for cost-plus charging, allowing the manufacturer to recover investment and a guaranteed rate of return.

The Industrial Biotechnology Association suggested that rather than focusing on fair pricing arrangements, a richer profit-sharing arrangement for the Federal laboratories should be agreed to by the National Institutes of Health and its industry partners.

Dr. Bernadine Healy has suggested that a clear pricing restraint preamble be added to the current cooperative pricing and research agreement signifying that the price of coproduced drugs is a threshold issue for entry into a cooperative venture.

The Chair is not wedded to any of these proposals, but I wish to note that the drug companies seem to be adamantly opposed to everything other than the status quo.

I believe strongly this issue is too important to get lost in the congressional fog. My principal interest is to work quickly now with my colleagues in the Congress on both sides of the aisle, the new Secretary of Health and Human Services, drug companies, patient advocates, and taxpayer groups to amend the technology transfer program so that new drugs get to the suffering as quickly as possible, but fair pricing is ensured as well.

[Mr. Wyden's statement may be found in the appendix.]

We wish to thank our witnesses for their cooperation. We look forward to working with them in the days ahead.

Three who have appeared before our panel before are here. I would like to welcome them and thank them for their patience.

Dr. Horovitz, Dr. Chabner, and Mr. Adler, as you know, it is the practice of this subcommittee to swear all witnesses who come before the subcommittee. So, let me ask you at this time, do any of you have any objection to being sworn as a witness today?

Please rise and raise your right hand.

[Witnesses sworn.]

Chairman WYDEN. Dr. Chabner, let us begin with you.

I am going to make your prepared statement a part of the record. If you can highlight in perhaps 5 minutes or so your principal concerns, that would be helpful.

Let me also take this opportunity to say that although we have disagreed on a number of occasions over the years, you have always been a pleasure to work with, most cooperative and professional, and we always welcome your appearance before this subcommittee.

TESTIMONY OF BRUCE CHABNER, DIRECTOR, DIVISION OF CANCER TREATMENT, NATIONAL CANCER INSTITUTE, ACCOMPANIED BY REID ADLER, DIRECTOR, OFFICE OF TECHNOLOGY TRANSFER, NATIONAL INSTITUTES OF HEALTH, AND MICHAEL FRIEDMAN, ASSOCIATE DIRECTOR, CANCER THERAPY EVALUATION PROGRAM, NCI

Dr. CHABNER. Thank you very much.

Mr. Chairman, members of the subcommittee, thank you for inviting me to testify before you today regarding the pricing of Taxol.

I am the Director of the Division of Cancer Treatment at the National Cancer Institute. I am accompanied by Mr. Reid Adler who is the Director of the Office of Technology Transfer, and by Dr. Michael Friedman, the Associate Director of the Cancer Therapy Evaluation Program. He was responsible for the clinical research related to Taxol and is here to help answer questions on that subject.

I welcome the opportunity to report to you on our experiences in collaborating with industry to develop the new anticancer drug Taxol. Specifically, my testimony will address the issue of the pricing of Government discoveries transferred to the private sector.

I would like to describe very briefly why collaboration with industry was essential for developing this drug.

As you know, Taxol was discovered by an NCI contractor in 1971. It exists as a minor constituent in the bark and needles of the yew species. Its purification to a form that can be administered to patients presents a formidable obstacle, and only a few quantities were produced by NCI in the early years of its experimental development.

The first signs of antitumor activity were reported in 1989. But further development and marketing required an industrial partner.

We could not afford or we could not offer market exclusivity, because the drug had not been patented. However, the Federal Technology Transfer Act did allow the negotiation of a CRADA, as you described.

In seeking a CRADA partner, we asked that in exchange for exclusive access to our data, our partner would be obligated to do the following: The partner would have to produce the drug in amounts required for research and commercialization; the partner would be required to cooperate with us in the executing of broad research agenda; and, finally, would be required to set a fair and reasonable price that would assure access for all patients needing the drug.

The CRADA was openly competed in 1989 and 1990. Only four applicants applied. Those included Bristol-Myers Squibb, a major international pharmaceutical company with a major interest in the field of cancer drugs.

The second applicant was Rhone-Poulenc, a major French pharmaceutical firm that had no track record in the cancer field but has patented and since developed Taxotere, a major competitor to Taxol.

The third was Lyphomed, a small American subsidiary of a major Japanese firm. The fourth was Unimed, a small company with very limited experience in the cancer field.

Bristol-Myers Squibb was chosen after careful deliberation of a committee of Government scientists, and agreed to terms with the NCI. The agreement contained a fair-pricing clause that recognized the Government's contribution and, at the same time, acknowledged the difficulty of production and the lack of patent protection.

However, the CRADA provided no specific guidance on how that price would be reviewed by NCI. I might add that the inclusion of this clause represented only the second instance in which a fair-pricing clause was included in a CRADA. The first being our licensing of the drug ddI, also to Bristol-Myers.

In that instance, the price of ddI, or Videx, announced in the spring of 1971, was far below that of the entry level of its competitor, AZT, and the company was publicly praised for its forbearance.

Since 1991, Bristol-Myers has fulfilled its contractual obligations with the aid of the Departments of Interior, Agriculture, and Congress. The company has been given access to yew bark on trees in Federal lands and now produces Taxol in commercial amounts.

Alternative semisynthetic sources have been identified and will free the company from dependence on the Pacific yew. Clinical trials supported by the partners have yielded evidence of consistent activity in ovarian cancer and promising early results in other tumors. Bristol has filed an NDA in less than 2 years, well ahead of the timetable set by the CRADA, and the Food and Drug Administration approved Taxol for treatment of ovarian cancer on December 29, 1992, approximately 6 months following the application.

Now, implementation or enforcement of the fair-pricing clause has required the NCI to consider several options. We considered the possibility of conducting a detailed cost base analysis of the proposed price, but rejected this alternative for the following reasons:

The CRADA, first, did not require the company to disclose proprietary information regarding cost of production and marketing, and the company affirmed its intention not to disclose such information.

Second, there are a number of unquantifiable factors that influence cost. These include a lack of patent protection in this case; the expected but uncertain future presence of a competitive drug, Taxotere; and the uncertain market size for the drug in its clinical development.

A third reason for rejecting cost-based analysis is NCI'S lack of expertise in pharmaceutical price setting. We felt such a policy would likely discourage further collaborations between Government and industry, and would undermine the intent of the FTTA, namely, to encourage the transfer of technology from the public to the private sector.

With the advice of counsel and the Office of Technology Transfer at NIH, we chose to measure the fairness and reasonableness of price by comparison with similar production.

We requested the company set the price below the median for other recently approved cancer drugs. We felt this was fair because, in our experience, Taxol was exceedingly expensive to produce.

From 1983 to 1991, prior to the CRADA, we produced Taxol for our own clinical trials, as we had similarly produced other drugs such as cisplatin for our own use. Taxol was at least 10 times more expensive to produce than cisplatin, the drug now considered the primary agent for ovarian cancer.

Beginning in the summer of 1992, we met on three occasions with Bristol-Myers to discuss their pricing strategy and emphasized the need to assure that all patients requiring the drug would have access to it. We believe their pricing strategy announced on December 29, is consistent with that goal for the following reasons:

The price meets the test of lying below the median for recently approved drugs. The wholesale price would lead to a total cost per cycle of $980 for the average patient, a cost less than the cost of carboplatin and less than other recently approved cancer drugs, such as deoxycoformycin, mitoxantrone, idarubicin, BCG, mitoxantrone, ifosfamide, G-CSF, and GM-CSF. Three drugs, zoladex, flutamide, and levamisol are priced less than Taxol, but are relatively simple molecules that can be produced by chemical synthesis.

We felt those unable to afford the drug would benefit from the provision that the company has established a very broad indigent program which will make the drug available free of cost to any patient unable to afford it.

Third, medical and Government institutions will receive the drugs at a significant discount.

Fourth, thousands of patients currently receiving Taxol under a broad compassionate-release program will continue to receive the drug after FDA approval.

Fifth, the drug for research trials sponsored by NCI will be continued to be provided free.

Sixth, consideration is that the price will be adjusted as indications for Taxol's use broaden and the market expands.

A seventh factor in our accepting this price as being reasonable is that the price in the United States will be lower than that in Canada, a significant factor that has been called to attention in recent studies of prices in the United States versus overseas.

The net-weighted cost of Taxol for American patients will be equal to the wholesale cost of cisplatin, despite the fact that cisplatin is inexpensive to produce and has been covered by patent protection for the first 15 years of its commercial sale.

Thus, we believe the pricing strategy announced by Bristol meets any reasonable test of fairness, if one considers these factors: The price of similar products; lack of patent protection; and the significant problems in its production.

In this instance, the Federal Technology Transfer Act allowed a very effective transfer of technology to the private sector, with all the advantages of rapid-scale production and commercialization, and with assured access of all women with ovarian cancer who require this treatment.

The success of this collaboration should offer strong encouragement to companies contemplating similar ventures, and this collaboration can only bring better health and a stronger economy to the American public.

You have asked our opinion as to the utility of a fair-pricing clause in our CRADA's. Based on our limited experience with such a clause, we believe it should be retained, and that it places a spotlight on price, and it puts the company on notice that its pricing policy will receive public scrutiny.

A second, and equally important provision is the statement of the principle of providing access for all patients who need the drug. This provision in the CRADA, in effect, provides leverage for establishing an indigent program and continuing to provide the drug under compassionate-release mechanisms.

In the case of Taxol, we believe our negotiations regarding a fair price produced the desired result. The issue of fair pricing of Government-discovered technologies has been further discussed in the December 2, 1992, meeting of the NIH Director's Advisory Committee, and we would be happy to provide a copy of the transcript for the record.

You have also asked for our opinions as to whether more restrictive pricing language would discourage cooperation between NIH and the private sector. We believe it would. In our recent experience, one company has refused to accept a fair-pricing clause as part of a licensing agreement for an anti-AIDS drug. A second company has done the same for a CRADA regarding an anticancer drug.

A third company has discontinued its collaboration with NCI in the development of a novel anti-AIDS drug because of fears the Government would use its involvement as a reason to impose price restrictions.

A fourth company has suspended negotiations for cooperative development of cancer drugs pending the outcome of these hearings. Another company has simply refused to become involved with us in early drug development, and although the reasons were not openly stated, I believe fears about price control played a significant role.

There is no doubt that companies will not accept the risk of investing large sums in the development of a Government product if their freedom to realize a profit is severely compromised. I do not believe they will be willing to put their cooperate fate in the hands of a Government-appointed committee of pricing experts.

There are probably less risky ways for companies to make a profit. As public officials, we recognize a responsibility to the American people and to the Congress to ensure their actions are in the best interests of public health.

We welcome the opportunity to appear before you today to address your concerns, and I would be happy to answer any questions that you may have.

[Dr. Chabner's statement may be found in the appendix.]

Chairman Wyden. Dr. Chabner, thank you, and I appreciate your testimony.

Dr. Horovitz.

TESTIMONY OF ZOLA HOROVITZ, Ph.D., VICE PRESIDENT, BUSINESS DEVELOPMENT AND PLANNING, BRISTOL-MYERS SQUIBB PHARMACEUTICAL GROUP

Dr. Horovitz. Thank you, Mr. Wyden.

This is actually, as you know, my second appearance before this subcommittee. When I first appeared in July 1991, I spoke about the many challenges, principally related to supply, that we and our collaborators faced in bringing Taxol to the market.

Today, I am pleased to report a number of major accomplishments: Taxol is now available to every woman in the United States who will need it. It is available at a fair price and access to Taxol is assured since we will supply it free of charge to anyone who needs it but can't afford to pay.

In addition, in less than 2 years, we have solved the Taxol supply problem. In fact, I can announce today that we do not plan to harvest pacific yew bark from Federal lands in the 1993 growing season.

There are many reasons for this record of what we think is significant accomplishment. We had the invaluable assistance of the NCI, certainly, the Forest Service, the Bureau of Land Management, Hauser Chemical Research, and a number of other collaborators, but we at Bristol-Myers Squibb believe we deserve credit as well.

How did these accomplishments happen? Immediately after the CRADA was signed, Bristol-Myers Squibb designated Taxol as our top priority in the company. We set four aggressive goals to meet the challenges that were before us:

First, to collect substantially more Pacific yew bark. Second, to provide NCI with clinical supplies of Taxol for research and treatment. Third, to develop alternative sources of Taxol. Fourth, to bring Taxol to the market as soon as possible.

Now, I never doubted the company's commitment to the project, and I never questioned our expertise in the development of anticancer drugs. But I was very concerned that these goals were too ambitious to be realistic 2 years ago.

This was based on the limited data that was available to us at that time. It was also based on the magnitude of these known challenges, and they were very great.

Today, however, I can state unequivocally that we have exceeded all of these goals. On December 29, 1992, less than 2 years after the CRADA was signed, FDA approved Taxol for use in the treatment of refractory ovarian cancer. Today, Taxol is widely available to women through oncologists and hospitals nationwide.

Now, the Taxol approval must be viewed as a milestone in at least two respects: First, and foremost, it ensured that a very important new anticancer agent was readily available in record time to patients. But in addition, Taxol is the first significant drug developed under a CRADA. Its approval provides tangible evidence that the CRADA process works as Congress intended it to; that collaborative research and development projects can yield meaningful results of measurable practical value to the American public.

For both of these reasons, the Taxol project really should be viewed as a model for future collaborations between Government agencies and private companies. This country certainly needs more of those collaborations.

The Taxol project also provides a valuable model with respect to the fair pricing of products developed under CRADA's. Why? Because it worked. It worked and struck a fair balance between the interests and concerns of both CRADA partners, the Government and the private company.

Now, in the remaining time, I will very quickly summarize just two points that were made in my written submission. First, existing NIH pricing policies are adequate to protect the public interest. The Taxol CRADA did not establish a formal process for evaluating price; however, building on experience gained in the pricing of Videx, or as it is known, ddI, an anti-AIDS drug also developed with the NCI by Bristol-Myers Squibb, we consulted informally with NCI on several occasions in the weeks preceding the Taxol approval. These informal discussions provided an opportunity for us to exchange information and share our respective concerns on issues described in the CRADA.

Bristol also provided two documents that I have submitted in my written submission. One is a lengthy analysis of key factors considered in setting the Taxol price, including the fact that we voluntarily relinquished orphan drug status.

The other provides a detailed description of the Taxol pricing structure. This includes information about Government discounts and rebates, as well as information about our patient assistance programs, which assure that no patient will be denied access because of inability to pay.

A product such as Taxol ordinarily would command a premium price compared to other comparable therapies in its class. Why? Because of its uniqueness, its life-prolonging potential, and the risks and extraordinary investment in Taxol's development.

However, the projected cost per cycle of Taxol therapy is well below that of many other recently introduced anticancer agents, even though it is not patented and has very limited exclusivity.

In fact, it is priced in the midrange of other agents currently used in the treatment of ovarian cancer.

All of these facts provide strong evidence that the price of Taxol is fair, and that, as I have said, the current process works.

The second point I want to make is there is no need for restrictive policies. They would pose a serious threat to the viability of the NIH technology transfer program.

Greater restrictions on product pricing would reduce incentives for private companies to participate in the CRADA process. Substantial financial incentives are necessary to justify an enormous investment, sometimes measured in hundreds of millions of dollars required for the rapid development of new pharmaceutical products. Few companies are willing or able to make investments of such magnitude. They want and deserve some assurance that they will have an opportunity to recover these investments and earn a reasonable return.

As a practical matter, any attempt to regulate prices will destroy the financial incentives necessary to attract private companies to these important collaborative research projects. According to NIH officials, and as you have heard from Dr. Chabner, several companies declined to become involved in CRADA's because of concerns about current pricing policies.

Many other companies, probably including my own, can be expected to withdraw from the process as well, if additional restrictions such as detailed pricing reviews are imposed.

In conclusion, in recent weeks I have been asked whether in light of our experience with Taxol, Bristol-Myers Squibb would agree to become involved in CRADA's in the future. I simply can't provide a definitive answer at this time. It will depend on whether the rules are significantly changed.

I can say that Bristol-Myers Squibb accepted unique challenges and exceeded every goal established under the Taxol CRADA. I believe the performance of the NCI, the other Government agencies, and Bristol-Myers Squibb has been exceptional, and that the Taxol project should stand as a notable example of public/private sector cooperation.

Nonetheless, at a time when the initial phase of the project is largely complete, and 2 years after the CRADA language was negotiated, some have suggested that new and different pricing obligations be imposed. In my view, any attempt to change the rules at this point would be wholly unjustified and manifestly unfair.

Finally, I must say, Mr. Chairman, in all candor, that the intense and many times uninformed public criticism which we, NCI, and the other collaborating parties have been subjected to, has caused us to question the wisdom of participation in similar projects in the future. Whether we will do so, remains to be seen. Whether others will do so will depend to a large extent on the precedents established by this project.

In fact, I really wonder whether there will ever be another Taxol developed by the CRADA process.

Mr. Chairman, that concludes my oral remarks. I am prepared for questions.

[Dr. Horovitz' statement, with attachment, may be found in the appendix.]

Chairman WYDEN. Thank you.

Let me start with you, if I might, Dr. Chabner.

One listens to your testimony, and I am just compelled to reflect on how arbitrary the pricing process seems to be. Bristol's Taxol price is 8 times the former cost of production to the Government. Cisplatin is 10 times as costly to produce as Taxol, yet, now they are being priced the same.

Now, it appears that there seems to be a very significant disparity between the pricing process and the cost of production.

You are shaking your head. Why don't you enlighten us.

Dr. CHABNER. The cost of Cisplatin is 10-fold less than Taxol. Their pricing strategy sets the average net-weighted price equally for the patient. So, Taxol is much more expensive to produce, yet it is being sold at the same price.

Chairman WYDEN. So, you would assert then there is no disparity between pricing and the costs of production?

Dr. CHABNER. In this instance, I think that one would have to say that the price is lower than one would expect for a comparable non-CRADA drug that would be marketed. I would have anticipated, for example, if there were no constraints on price, given the additional cost of production of this drug, that it would have been priced significantly higher than it was.

Chairman WYDEN. Well, what about Bristol's Taxol price being many times the former cost of production to the Government?

Dr. CHABNER. The price includes many other factors besides cost of production. For many drugs that are marketed, the cost of production is a very small component of the price. There are the costs of advertising, the costs of distribution, and profit. There is corporate investment in marketing; a number of different factors.

In this case, the investment for the company upfront to manufacture the drug, not the simple cost of producing the drug each time in a vial but the basic investment, is very high. The CRADA calls for an investment of over $115 million, and they have exceeded that.

So, I think that this price does compare very favorably with other drugs that are currently on the market.

Chairman WYDEN. You have said, and we certainly think it is the case, that a big part of the price deals with advertising, marketing, and things of that nature. But what percentage of the price deals with the costs of production? I ask because we see that Taxol's price is many times the former cost of production to the Government.

I appreciate you giving us your assessment of the cisplantin example. But on the Taxol issue specifically, there is no question that Bristol's Taxol price is many times the former cost of production to the Government. It would be helpful to know in this particular instance what percentage of the price was due to production and what percentage was due to these other things, such as marketing, advertising, and the like?

Dr. CHABNER. My estimate of this, based on my experience of producing Taxol, is that the cost of this drug without all these other factors taken into consideration, is probably in the range of 25 to 35 percent of the marketed price of the drug. For other agents such as cisplatin, the cost was probably in the order of 5 to 10 percent, and that is just a guess, maybe even less.

Those production costs for Taxol were much higher, and I think were a significant portion of what is being charged.

Chairman WYDEN. So, of the price that is being charged for Taxol, between 65 and 75 percent of the price, in your opinion, goes to marketing, advertising, distribution, and other nonproduction matters?

Dr. CHABNER. That is right.

Chairman WYDEN. Is it true that funds go into analogues, similar drugs, and the like?

Dr. CHABNER. That is true, and it also will go into development of alternative sources. I think these questions probably could be best handled by Dr. Horovitz, who represents the company. These are just my impressions of how the price is formulated.

Chairman WYDEN. We intend to ask Dr. Horovitz a number of these questions as well. It has been very difficult to get any of this kind of information. This is particularly important because if we are going to strike a fair balance here, which I think everyone agrees is the challenge, to get drugs out quickly, but to ensure that they are fairly priced, we have to get some handle on what amount of the price goes for production and what goes to these other things. I can assure you that my constituents would think that to have 65 to 75 percent of the price of a drug going for marketing, advertising, and other things, for a drug that really sells itself, when people are so desperate to have it, seems fairly high. But we are going to explore that question a bit further.

Now, do you have any handle on how much Bristol may have spent, again relative to the production price, on trying to develop synthetic Taxol, analogues, similar drugs, and the like?

Dr. CHABNER. I can't tell you about analogues. I know that their total investment in Taxol's development exceeded $115 million. What portion of that was for analog development, I can't really answer. You would have to ask them.

They have supported a number of initiatives to find alternative ways of producing Taxol itself, which is, I think, very important, given the source being the trees, and they have been successful in doing this.

Chairman Wyden. Do you think that Federal dollars ought to be used in that fashion, given the fact that lots of other companies are trying to get access to the analogues, the similar drugs, and the competitive products?

Dr. Chabner. I can't speak to how Bristol-Myers——

Chairman Wyden. I am talking about from a public policy standpoint.

Dr. Chabner. We are supporting a great deal of research on the synthesis of Taxol and its analogues. The analogues synthesized under this program will be patented and will be available for licensing to other companies and represent, in fact, potential competition for Bristol-Myers.

Chairman Wyden. That is good because it ensures that the taxpayers' investment is truly recouped.

My question is, do you think that a company like Bristol-Myers should be able to include in its production and overall pricing some of the research costs of these other analogs, when other companies simply have to pay their own way?

Dr. Chabner. In fact, I think that it is to the benefit of the public for them to do this because it is certainly possible that an analog could be a better drug than Taxol and would solve some of the problems associated with Taxol.

I don't mind this, that they would use corporate profits to invest in research. I think this is important.

Chairman Wyden. Tax credits, not corporate profits. We are talking about one company being able to possibly use tax credits to get to the next level and solidify its monopoly.

Dr. Chabner. It is not clear to me what tax dollars you are talking about, Mr. Wyden.

Chairman Wyden. I am returning to free development costs financed through tax dollars for research performed by NCI when the contract shows Bristol-Myers already has a leg up on new research and new data.

Dr. Chabner. This is only on Taxol. They don't have access to any of our research regarding analogues. Our research regarding analogues belongs to us, and we will license it to other competitors.

Chairman Wyden. Are you saying that none of Bristol-Myers' research and development investment is being used to acquire patented technology for analogues?

Dr. Chabner. What they do with their money and their profits is not something I control.

Chairman Wyden. But no tax dollars are being used in that fashion?

Dr. Chabner. No.

Chairman Wyden. Are you certain of that? I find it hard to understand how you can be certain of that, given the fact that we have gotten so little information with respect to the pricing practices.

But why don't we do it this way. Bristol-Myers Squibb has said it has made a huge investment in Taxol; $114 million. Could you break down for us where that $114 million has gone in terms of development. Dr. Broder wrote me that you all developed it, so, I am curious about whether they have any development, testing, marketing, or distribution costs. Where has that $114 million investment that Bristol-Myers claims to have made gone to?

Dr. Chabner. The most visible product of that is the fact that there is about a 40-fold increase in the amount of drug that was produced by them as compared to us. I think that is a major component of that production pathway.

There are other costs we are aware of. I think if you want a breakdown of the costs of their investment, where their investment has gone, you really need to ask them, because I don't have a breakdown of the $115 million.

Chairman Wyden. NCI gave them the green light to charge close to $1,000 for a 3-week treatment cycle but NCI says that it really doesn't have any decent information about the pricing; is that correct?

Dr. Chabner. I have the information of our experience to compare to the price that they have charged, and it seems to me, given the fact that this is an expensive drug to produce, and I know approximately what it would cost to produce it for us, that their price seems reasonable to me.

Chairman Wyden. But it is arbitrary——

Dr. Chabner. Certainly it is. We have not done a detailed cost analysis based on a look at their books. I think your opening statement really said it pretty well, that the Government currently does not have the expertise to do such an analysis, nor the legal right.

Chairman Wyden. Dr. Chabner, the model CRADA's fair pricing clause gives NCI the option to require the firm to submit information showing that a price has been reached in a reasonable fashion. Why doesn't the clause require submission of information relative to the companies' investments and risks?

Dr. Chabner. That wasn't put in. I can't answer that question, Mr. Wyden. Maybe Mr. Adler could answer that. The model CRADA really came out of the Office of Technology Transfer.

Chairman Wyden. Mr. Adler.

Mr. Adler. When the reasonable-pricing clause was developed in the spring of 1989, the NIH Patent Policy Board, and its administration representatives higher in the Department of Health and Human Services, particularly at the Assistant Secretary of Health level, were concerned that the public investment in the development of products through CRADA's, or through licensing agreements, was reflected in the product's price and availability. At that time, we articulated at the least a principle and focused attention, not only of our own scientists and administrators but companies, on the relationship between the public's investment and what it gets out of a CRADA project.

This particular process, as you know, has been a focus of a great deal of congressional and NIH attention, and it has been evolving over the last few years.

So, the reason why, to give you the direct answer to your question, that the clause didn't ask for a list of other types of factors, is that we tried to articulate a broader principle and then work with it over the next few years to see what recitation of clauses or promises would be appropriate in the public interest. I think that Taxol is a very important case study for us in that regard.

Chairman WYDEN. Mr. Adler, when Dr. Healy testified before the subcommittee 14 months ago, she talked about pricing issues and said that you were heading up a special multiagency task force on the status of pricing language in model CRADA's. Can you give us a quick rundown of what has happened in those 14 months?

Mr. ADLER. Yes, Mr. Wyden; we have held several meetings of the working group that included representatives of a number of different agencies. We have had consultations with industry trade associations and with the academic centers that study pricing related issues. We have developed a number of legal issues that the Office of General Counsel is exploring in this regard and have developed a range of options, many of which you articulated in your opening statement.

This issue was presented to the NIH Directors Advisory Committee early in December, and we are now in the process of preparing a fairly detailed analysis paper, an options paper for use by Dr. Healy and others in the Department.

Chairman WYDEN. Maybe you can enlighten us on the practice of simply taking one drug and saying, "We will price it in line with a similarly situated drug."

How did that happen to become the agency's position for dealing with these kinds of pricing matters? My constituents question the prices of lots of drugs that are out there now and consider them excessive them to be told that instead of trying to get a pricing justification, we must go out and get what we think is a similar drug that may be priced in a similarly arbitrary fashion, is not acceptable to my constituents.

How did it happen that the agency came upon this process of just using arbitrary pricing in these kinds of decisions considering that one arbitrary price is essentially the standard for all other drugs?

Mr. ADLER. It is not accurate to describe this approach as the agency policy with respect to pricing matters. It is——

Chairman WYDEN. It is, in fact, what was done in the Taxol case, is it not?

Mr. ADLER. That is correct. Yes.

Chairman WYDEN. What is the agency's policy?

Mr. ADLER. To the best——

Chairman WYDEN. Does the agency have a policy?

Mr. ADLER. I have——

Chairman WYDEN. Other than saying only that we will trust the drug companies, let them do what they want, and do whatever they think is just fine? Is that the agency's policy?

Mr. ADLER. That is something I can't tell you. I don't speak for the agency at the moment. The new administration, the new Secretary, and we are working to analyze options and issues and legal authorities on a number of issues that have come up at your previous hearings. I don't believe the department is ready to announce a policy on this.

Chairman WYDEN. What has been the agency's policy? I have described what was done in the Taxol case. You first said that was correct and then you said that is not necessarily the agency's position. Please tell me what is the agency's position if it is not just to pull an arbitrary figure out of the air and say, "That sounds as good as anything else, let's charge that."

Mr. ADLER. As Dr. Healy told you at the hearing in December 1991, this is an issue that has the public health at stake, and it has tended to move very prudently and be analyzed very carefully. The implications of the agency's approaching to pricing, the Taxol CRADA, and the negotiations between NCI and Bristol has been a very important case study in the development of the policy. I don't believe that the department has a final policy ready at the present moment.

Chairman WYDEN. Does the department have any other policy than what they are using in the Taxol case? The Taxol pricing policy seems to me to be wholly arbitrary and based on a kind of rough assessment that another drug is similar, thus Bristol-Myers will price Taxol the same?

Mr. ADLER. Dr. Chabner, I think, has very clearly described the factors and considerations that were considered by NCI in its evaluation of the price. I think that a statement from the department probably will have to await further assessment of the issue by Secretary Shalala.

Chairman WYDEN. I have some additional questions for you Dr. Chabner. Suffice it to say, since the department does not have a policy as of today, we will ask Dr. Shalala to tell us what the department's policy is going to be. Hopefully, it will be a policy that does get some reasonable cost data from the companies, unlike the previous policy.

Now, Dr. Chabner, Bristol-Myers Squibb has indicated that it considered factors in addition to production and marketing of Taxol in setting the price. These factors included a program of free drugs for the indigent and the Government's contribution to Taxol's discovery and development. Can you tell me how these factors related to your determination of Taxol's price?

Dr. CHABNER. Yes; I think they were important because I think the major issue for us is that all patients should have access to this drug, and we feel that the pricing strategy, including the indigent clauses, were comprehensive, that all patients, I feel, will have access to it.

How did they affect our analysis? In a major way. They had an effect because the wholesale price of $980 per treatment cycle must be reduced when one takes into account the amount of free drug that has been provided. If one does that, the net average price for patients is about $700 per treatment cycle.

Now, I agree with you that we don't have the precise information on all the factors that go into the price. In fact, I don't think it is possible for anyone to put numbers on all these factors. Any drug that is in the marketplace is priced based on educated guesses by the company, plus the profit factor. I think it would be very difficult for a Government agency to dissect these prices.

I think here we probably do know a lot of the bare facts about the drug in terms of its difficulty of production, its lack of patent protection, and the size of the initial market.

Now, really, we have to ask ourselves a question. Are we going to benefit the process of technology transfer and benefit the public health by making a more arduous pricing policy, or does the current way encourage companies to get involved and bring products to the public? It is my feeling that if we significantly tighten the pricing policies related to CRADA's, that we will discourage technology transfer. That is an experiment which the Congress can do if it feels that it is indicated, but, based on our experience, I think it will have an adverse effect.

Chairman WYDEN. If you all are interested in cost factors relating to the indigent, why aren't you interested in cost factors relating to the price that the vast majority of people are going to pay when they have to pay for it through their insurance?

I think it is very good that you are interested in cost factors related to the indigent. I am for it. I support the agency's position in that regard. Bristol-Myers is doing the right thing in terms of trying to help the indigent.

What I am puzzled about is why, given your interest in the indigent, you wouldn't be interested in similar kinds of cost considerations as they relate to the vast majority of people. We all know the vast majority of people are going to pay for it through their insurance. Unless agencies like yourself get hard-nosed about obtaining price data, prices will just be based on the spiraling upward trend of health costs we have.

Dr. CHABNER. Well, Mr. Wyden, I think that we are interested in this data, but we asked for it, and we don't have the legal right to acquire it, and that is a problem you had addressed.

Now, whether that will, in the long run, benefit us and the public health to have that kind of information and to potentially discourage companies from getting involved, I don't know. We just don't have access to that precise data.

The second factor, as I mentioned, is that it is hard to put numbers on some of these factors.

Chairman WYDEN. Do you all have any idea what level of profit Bristol-Myers is making on this drug, particularly during the period between now and 1995, when there is hope that there may be some alternative?

Dr. CHABNER. I don't know precisely what profit they are making on this. I presume that it is enough to keep them interested, and I just can't tell you beyond that. I know the average profit of the industry for drugs is somewhere in the neighborhood of 8 to 10 percent of sales, and whether that applies here, I don't know. But since its price is about the same as other drugs on the market, and its cost of production is higher, I would estimate the profit is in that range.

Chairman WYDEN. Let me also ask this. I know free amounts of this drug are given to the doctors for marketing. Is that subsidized by the wholesale price?

Dr. CHABNER. We aren't giving free amounts to doctors. We are giving free amounts to patients who are on compassionate protocols, and that is part of the agreement. We refer indigent patients to Bristol-Myers who get it directly from them.

Chairman WYDEN. Are doctors getting free amounts of this drug for marketing?

Dr. CHABNER. No, they are not.

Chairman WYDEN. Our understanding is that free amounts have been given to doctors for marketing purposes. Dr. Horovitz, is that correct?

Dr. Horovitz. I can't answer that question. I don't know if any of that has happened. There is free material provided for patients if the doctor calls us and indicates that a patient cannot pay for it themselves. That material is provided free.

Chairman Wyden. My understanding is that for virtually all new drugs, free amounts are to doctors for marketing and promotional purposes. We will follow this up if you all are not familiar with this practice.

Dr. Chabner. I don't think that happens with cancer drugs. It may happen with other drugs where they get professional samples—for example, ulcer drugs or things like that—but I can't imagine that cancer drugs would be given that way.

Dr. Horovitz. That is correct. It is not the practice in oncology.

Chairman Wyden. The National Cancer Institute is currently assisting development of Taxotere. Because Taxotere is a likely competitor with Taxol, does the National Institute of Health have cost of pricing information on Taxotere that could help in assessing the reasonableness of Taxol's price?

Dr. Chabner. We don't. We asked them to include a fair pricing clause in the Taxotere CRADA, and they refused to do that. They did not want any disclosure of pricing information or any Government pressure about pricing relating to Taxotere. So, we were left with the option of either not having an agreement with them and letting them develop it on their own or encouraging them as a competitor of Taxol, and we chose the latter.

Chairman Wyden. Dr. Chabner, we have sparred on a number of issues. I appreciate your clarifying the matter.

We will look at a variety of other issues related to marketing and the like. Taxpayers are very interested in knowing what you can tell them about their return on a very substantial investment. Today's topic is particularly important in this era of belt tightening and deficit reduction. We are going to have a number of witnesses come today. They are going to say Bristol-Myers Squibb did very little to try to get this product out to the public. They are going to say that the Government did much of the heavy lifting.

Now, it seems to me that unless you as the agency that has worked most closely with this can give us some information so that taxpayers can know what their return on investment is, the taxpayers are going to want a lot more accountability in this area. What can you tell us about what the taxpayers have gotten as their return on a very substantial investment?

Dr. Chabner. The taxpayers have gotten a terrific drug in a matter of 2 years under this CRADA and a very cooperative partner from an industry that has fulfilled every aspect of this CRADA, including the pricing clause, as written in this CRADA. They have proposed to market this drug at what I think is a reasonable price. It is the same price as other drugs which are much cheaper to produce.

Beyond that, I can't provide the taxpayers with a detailed breakdown of the costs and the financial status of Bristol-Myers as a company, and I doubt if you are going to get any company to cooperate with the Federal Government if this is the price for cooperation.

Chairman WYDEN. Well, I am going to ask Bristol-Myers these questions. You can't provide us with some reasonable assessment of where Bristol-Myers' $114 million investment has gone and you haven't even asked. That is what I was told in the 1992 letter.

I just think taxpayers in an era of skyrocketing medical costs are going to require more accountability. My concern is that we keep this technology transfer, the good part, the part that gets the drugs out quickly, but that we address the part which has been festering as a growing problem in our country. The problem is that if Americans don't want to get sick, they must run the risk of getting gouged, and that is not acceptable.

You have told us everybody ought to be happy because the price of Taxol is going to be about the price of other drugs that you consider similar. Well, I guarantee you if you come to one of my town hall meetings, citizens will tell you that they think that the price of those other drugs is too high, and it is not going to be acceptable to just continue this merry little process that says, "everybody be content with what you got because it is priced in the vicinity of some other drug."

We will, I know, have many other conversations on this subject in the days ahead. I thank you for the cooperation you have shown.

Now, Dr. Horovitz, let me turn to you, if I could.

Dr. Broder wrote me that Taxol, and I quote, "was discovered and developed within the National Cancer Institute's comprehensive anticancer drug development program." Do you disagree with that statement that Dr. Broder made?

Dr. HOROVITZ. Well, we may have some difference as to the definition of development, Mr. Wyden. Certainly, the NCI did a fantastic job in the discovery of Taxol and bringing it at least to a point where there was some enthusiasm for it to go further. However, as I have said, NCI stalled. They stalled because they weren't able to get material, they weren't able to get enough Taxol to prove whether it really was a unique kind of compound, and that is where they started looking for their commercial partner.

There are many other things that go into the development of a compound like Taxol that occurred after the NCI selected a partner and after we negotiated the CRADA, and Dr. Chabner has gone through them. He didn't mention the large capital investment needed to scale up so that we could produce kilograms, not just grams, of material which the NCI has received. He didn't include the good manufacturing practice costs that you need when you scale up and have to go through the FDA. He didn't include all the regulatory costs.

Additionally, it has been discussed that there are distribution costs. The NCI was providing material to just a few centers. We have to provide it to every oncologist and treatment center that needs it throughout the country.

There is physician education. In this case, I don't call it marketing. I don't think there is the same kind of marketing with oncology drugs as, let's say, a hypertensive agent, but there is education of oncologists.

Although most physicians have heard of Taxol, the majority of the physicians have never used it, have never had the experience of using it, and don't know how to use it. That information is important for us and the NCI to try and get across in the next year or two.

We must pay royalties and fees to our collaborators. They want some return on their investment, and those can be huge. We have done a lot of work on alternative sources.

I can go on and on, but let me finish with one more example. The company, whether it be Bristol-Myers Squibb or any other partner in the CRADA process, demands a return on its investment, not only for what it has spent on the product itself, but also for continuing to maintain a basis of research and development expertise so that when something like Taxol comes along there is an infrastructure that can be immediately put to use so promising that drugs can be developed quickly.

All of these things went on after the CRADA was negotiated with Bristol-Myers Squibb. Although the NCI continued to contribute, and we consider Taxol development a partnership, we had great expenses. In fact, that figure of $114 million was not our total cost of development. We have exceeded that by many millions. That is just the cost that was identified in the CRADA as something we promised that we would spend. We have spent many, many more times that figure.

Chairman WYDEN. Well, why don't you break out for me then how all these various factors which you describe produced the situation which justifies a price of six to eight times what the Government initially paid?

Dr. HOROVITZ. Well, I am glad you raised that figure, Mr. Wyden, because it is an example of a use of comparing apples and oranges, and I——

Chairman WYDEN. Part of the problem, Dr. Horovitz is that as long as you are never willing to provide any real fruit to the Government so we can do a decent pricing comparison, then we are going to have to go on these small shreds, these shreds of information that you and your associates wish us to go by. We wish to be supportive of a process that gets drugs to our citizens quickly and reasonably priced and allows people like yourselves to make a reasonable profit.

I have supported every conceivable kind of incentive for companies like yourself, whether it is corporate tax credits, research and development tax credits, et cetera. I am one of the Democrats who voted for product liability reform that you and your associates in the pharmaceutical industry wanted. We have been willing to support a vast array of incentives for people like yourself.

You say that we are comparing apples to oranges, but give us some fruit on this pricing issue. Then, I can assure you that you will be treated fairly. But as long as you wish to charge these prices that seem so exorbitant to my constituents and then justify them with just the vaguest generalities, you are going to find that is unacceptable.

Dr. HOROVITZ. Thank you, Mr. Wyden. I will give you the description of an apple and an orange. The difference here is that, first of all, Dr. Chabner has said many times that their cost approximated 90 cents, not 60 cents as was used in the press and in——

Chairman WYDEN. We have said 60 to 90 cents.

Dr. HOROVITZ. I think 90 cents was the latest figure.

Second, that has to be compared to our average net price which is $695 and has been properly detailed in my submission. That is after you factor in the wholesale price, the Federal discounts which can go up to 24 or 25 percent, all the discounts to physicians, all the discounts to the Public Health Service, and giving away the product free, not only to the patients who need it but also to the NCI for all the clinical studies that they would like to do.

So, if a price comes in well below—if you divide 90 into that price per course, you come well below the figure that has been used, probably less than half that multiple.

Second, Dr. Chabner has given you a price of approximately $250 or a little less than that for a cycle of treatment. You and some of the others have indicated that our price should be $100 to $200; I think it is easy to see that we would be losing money at that price.

Finally, we have all of those other costs; the cost of production is only a portion, as Dr. Chabner has said. We have all of those other costs that we have put into making this a drug that is available to patients in a short period of time. All those have to be taken into consideration.

Chairman WYDEN. Well, Dr. Horovitz, you are simply misstating the record. I have said only that until there is a decent cost analysis done, if you are going to be in the arbitrary pricing business, Government ought to be on the side of protecting the consumer and the price ought to be at the bottom range of cancer drugs rather than the middle range or at the top. When we get a decent pricing analysis, I think you will find that many of us who have had an interest in this matter want to see you treated fairly.

Now, you note that part of the price that we pay supports the company's ongoing research for new R&D. Now, that is done for defense contractors as well, but the Government purchases a number of their goods on a cost plus basis. Is your company willing to look at that kind of cost plus pricing as a way to extricate this thorny dilemma and insure drugs get out there quickly and are fairly priced?

Dr. HOROVITZ. Mr. Wyden, I can't comment on that. It has never been discussed in my company. There is no way I can respond to it.

Chairman WYDEN. Has anything been discussed other than stonewalling the public?

Dr. HOROVITZ. Yes, Mr. Wyden.

Chairman WYDEN. I ask because there are a number of alternatives, all of which strike me as worth debating. I have indicated that I am very open to working with the industry. However, what I find is that the only position that you all have said is that the American people don't get to know. You charge them; they pay the price. If they don't pay the price, they get sick. I would be very interested in knowing whether there are any kinds of alternatives that you all might be willing to look at.

Dr. HOROVITZ. Mr. Wyden, we take the position that the price of Taxol is fair based on the CRADA, and the CRADA had two important aspects in the pricing clause. The first was that we take into consideration the Government's investment.

Now, as I said in my oral presentation, Taxol ordinarily would have demanded a premium price. It is unique. It has possibly life-saving or life-prolonging activity. Normally, another company that had not worked with the Government if it was their patent, they would have priced Taxol at a premium to what was out there already. That is market pricing.

We have not done that. We have priced it in the mid-range between other drugs that are used for ovarian cancers. Indeed, we have priced it well below new oncology products that recently have been approved.

The second aspect is we promised through the CRADA to think about the public's health and safety, and we think that we have done that in two ways. We put every effort possible into getting Taxol approved in record time, much less time than was promised in the CRADA. Second, we have provided the drug so that no patient will be denied access to it if they can't afford to pay, and that, to us, is the definition of fair. That is in the CRADA and was negotiated with the NCI.

Chairman WYDEN. How does the taxpayer, in your opinion, Dr. Horovitz, know whether this is a fair price?

Dr. HOROVITZ. First of all, I would answer that by saying I believe you do the NCI a disservice when you don't recognize that they understand the development of oncology products. They have tried to make Taxol and other anticancer drugs. They know what is involved. They are practicing oncologists, most of them, and they understand the treatment of patients and the marketplace, and I think they have done a good job.

Chairman WYDEN. NCI has already said here today that it knows virtually nothing about how this drug was priced.

Dr. HOROVITZ. They said they know nothing about some of the factors that come in later in the development process as I have described because they are not involved in it, but they do know a lot about the development and the cost of producing Taxol, and they have made a judgment, based on the best way that they think and the CRADA indicates, that this is a fair price. I think as a Government agency they are trying to do the best they can, and the public should trust them. I think they have done a fantastic job in the cancer field, and I think the public should trust them.

Chairman WYDEN. So, the public isn't going to get the information from you as to why it is a fair price, and you are not going to give the information to the National Institutes of Health, but citizens ought to pretty much just trust everybody because you all are nice fellows?

Dr. HOROVITZ. Mr. Wyden, the citizen should be very pleased that a Government invention was developed early and provided to patients in record time. I think that is very important for them. They also should be pleased that none of them will go without Taxol because they can't afford to pay. I think that is very important to the public, and those were the things in the CRADA that we negotiated and felt were important.

Chairman WYDEN. We are very pleased about those developments as well, Dr. Horovitz.

Dr. HOROVITZ. Thank you.

Chairman WYDEN. What we are concerned about is whether or not the vast majority of people who are going to pay for Taxol with their insurance, and the like, are being treated fairly. Other than "trust you" and "trust the good Dr. Chabner," who is a fine individual, I have heard very little that would give citizens any comfort in knowing how these drugs were priced.

Now, could you tell us how you break out the huge investment that you all have made in Taxol, the $114 million? Can you give us a rough idea how much has been spent? There are really four areas: Developing, testing, manufacturing, and marketing. Can you give us a rough idea of the amount of funds allocated for each?

Dr. HOROVITZ. Mr. Wyden, I think our company has indicated in the past to you that that is proprietary information. We deal in a very competitive pharmaceutical market. There will be a competitor to Taxol, Taxotere, which is being developed by the French company, Rhone-Poulanc Rorer which probably will be on the market within 18 to 24 months. Not only is that confidential information that I think the courts have upheld we should not share with the public, but I do not think that it is in the public interest to release that information. Because I think what everybody knows is that if your competitors know our costs they can avoid competitive pricing.

Chairman WYDEN. Well, I think it is ironic that you all are very willing to give out confidential information when you think it serves your corporate interests and it helps public relations, but when Members of Congress want a rough idea so that they can get a handle on these costs, you aren't willing to do it.

Now, as you know, you all claim that your overall investment level and the number of your research years and research man hours, was confidential early on. I am informed that recently you all have been going out to newspaper editorial boards and others and telling them about this information that you previously claimed was confidential. So, it seems to me that whenever it serves your corporate interests, you are plenty happy to talk about confidential information, but when it is going to address taxpayer concerns, such as how this drug is priced, then you get back behind the veil and say "no, no, no." That is not in the public interest.

Dr. HOROVITZ. Mr. Wyden, I think you are misinformed. What we talked about, those two factors, what we spent and the man years we put in R&D, were part of the CRADA and the partners' discussions, and all we have said is we have exceeded both of those factors, because they were a promise we made to the NCI. I think the NCI appropriately asked us to promise a certain effort. That is called due diligence when you do an agreement, and I think that is appropriate for the Government partner to ask for, and we gave them some estimates of that due diligence and what we would do, and we have assured them that we have exceeded the due diligence requirements that we promised them in a short period of time.

Chairman WYDEN. Well, the point is, in the CRADA there was a specific research dollar figure that was supposed to be secret. I know we were informed of that amount. We kept it secret. Then we learned that when you all felt you had exceeded the number you were happy to go out and talk to newspaper editorial boards about it. Isn't that correct?

Dr. HOROVITZ. We first told the National Cancer Institute that we had exceeded the requirements in the CRADA, and we agreed together that was something that we would not keep secret any more.

Chairman Wyden. But it was kept secret originally. Wasn't that a public relations benefit to you to be able to say right before the hearings that you were going to come on in and claim that you have exceeded the overall investment figure? I mean, you all made a big deal in terms of our getting access to the CRADA about that overall investment figure being secret, confidential. We honored that. We were given that figure, and we kept it secret. Then you all, when it served your public relations interests, got permission from NCI to go on out and talk about it. Isn't that what happened?

Dr. Horovitz. I don't understand the secrecy that you are claiming. Yes; before we would say anything we would discuss it with our partner, the NCI. Once it was agreed to let the information out, it was let out. I believe that our company has the right to tell the public the exact facts about the Taxol project. I think our partner, the NCI, agrees with that, and they encourage us to tell as many facts as we can, and we have done that.

Chairman Wyden. Well, since you all will say nothing about your costs of this so-called huge investment in Taxol as it relates to development and testing, manufacturing and marketing, let me ask whether you are willing to tell us how much, if anything, was spent on developing analogs and similar products and new sources.

Dr. Horovitz. That is also, obviously, proprietary information. We believe that we have the obligation to try and improve on Taxol, if it can be done. We don't know that it can be done. We will not market a product that isn't an improvement on Taxol, and we are doing some research in that regard. It is a small fraction of the amount that we have already spent on the development of Taxol itself, and it has nothing to do with Government funding.

Chairman Wyden. Well, you said two things. No Government funds, then, are being used on anything relating to a new source, synthetic, analog, or anything of that nature?

Dr. Horovitz. That is correct. The Government is not giving us any money.

Chairman Wyden. But how does the Government know that you are not doing work that may promote those other areas? I mean, the reason for this—and your competitors are obviously very interested in this as well—is that the great hope of all concerned is that in 1995 there are going to be synthetics, analogs, and all kinds of alternatives. But they are not getting any kind of support from the taxpayer for their development. You are going to your investors in order to be able to explore these new sources? Now, I heard you once say that a tiny fraction was being devoted to analogs and the like, and then you said no Government money.

Dr. Horovitz. That is right. The fraction I was talking about is what we have spent on Taxol. We don't calculate the Government's expenditures on Taxol. We have spent all this money ourselves. There is no Government funding in that figure. That is our spending, Mr. Wyden.

Chairman Wyden. With regard to your marketing expenses, Taxol, the most promising new cancer treatment in 15 years, subject of extremely wide media exposure, would seem to be a drug that virtually sells itself. Why do you all need to spend so much money on marketing?

Dr. HOROVITZ. Well, I never said we spent so much money on marketing. I didn't give you a figure, Mr. Wyden.

Chairman WYDEN. That is the point. Why don't you give us one?

Dr. HOROVITZ. The reason we have to spend some money on marketing is that, as I told you, most oncologists have never had the opportunity to use Taxol. They have heard about it in the press. Maybe that is a bad thing, but they have never been able to use it. They don't know really how to use it, and it is going to be important for us to educate them on the proper way to use it, its abilities and its limitations, of which there are many.

Chairman WYDEN. Why don't you tell us how much you are spending on marketing? I mean, I am going to walk out of here and you will have only used again the figure of $114 million.

Dr. HOROVITZ. Over $114.

Chairman WYDEN. There has been a huge public investment, but you won't tell us where a penny of your investment has gone because all that is proprietary. You won't even tell us about things like marketing. Why not?

Dr. HOROVITZ. Mr. Wyden, I have to correct you. More than $114 million is what Bristol-Myers Squibb has invested, without $1 dollar of public money, and I hope you understand that and don't insist any more that that figure relates to a public investment. It is not. It is Bristol-Myers Squibb's stockholders' investment. It is over $114 million.

Chairman WYDEN. No one has ever said that the $114 million is a public investment. You all repeatedly cite that as, in effect, minimizing the Government's role and magnifying this great contribution that you all have made.

My constituents look at the statement of Dr. Broder who says that the Government discovered and developed it. They look at that list—that very lengthy list—of what the Government did. They look at the amount that the taxpayers put in, which was over $30 million, and they say, holy Toledo, it looks like the Government did all the work. How many times are we going to have to pay for this drug?

What did Bristol-Myers do? You come to us. You say, we spent $114 million of our own money. That sounds like a lot of money. I am dying to know how much of that sum went to actually getting Taxol out there to fight ovarian cancer. Since you won't tell us, it makes one a little bit suspicious.

Dr. HOROVITZ. I will tell you, sir, and I think I have told you—I have told you that every dollar plus multiples of that have gone strictly to develop Taxol, including an alternative source to be able to produce it without cutting down trees. That is where that money has been spent, and I think we have been very clear in saying that. It is important to the patient to know that we were able to do this in record time so that Taxol could be made widely available, and I seriously doubt whether that could have been done without a major investment, or by very many other companies.

Chairman WYDEN. That may well be the case. It may well be the case that this couldn't have been done without you, and we have acknowledged that is a possibility. It also may be the case, Dr. Horovitz, when you look at all that Dr. Broder has told me that has been accomplished at NIH, that you all may not have done a whole lot except put it in that pretty little box that you have been holding up. Now, I am anxious to have an answer to that question.

Dr. Horovitz. I think Dr. Chabner——

Chairman Wyden. You are a sincere fellow.

Dr. Horovitz. Thank you.

Chairman Wyden. I think that there are certainly some things you all must have done other than put it in that pretty box which you wave around repeatedly. But unless you are willing to tell us what those are, all we know is what Dr. Broder says the NIH has done. When I am done reading that, I say to myself, it sure doesn't sound like there was a whole lot left for Bristol-Myers to do.

Dr. Horovitz. Mr. Wyden, I will go through the list again of the things we have done. We have made a tremendous capital investment in scaling up the production of Taxol from grams to kilograms so that every woman who needs it can get it. We have responded to the need for complying with good manufacturing practices on a large scale, and all of the research that goes to scaling up Taxol production. We have contributed all the regulatory effort and cost that goes into pulling together all the information, including clinical, preclinical, and pharmaceutical support, making the NOA filing, and working with the FDA.

We have the responsibility of distributing Taxol throughout the whole United States, not just to a few treatment centers, which was the NCI's responsibility. We have physician education, and we have discussed that. We have royalties and fees to pay to our collaborators. We have done a tremendous amount of research on alternative sources.

There was pressure on all of us, the oncology community, Bristol-Myers Squibb, and NCI. Certainly your committee did an excellent job in bringing up the issue of yew ecology, and we have responded to that by paying for new ecology studies with the Government agencies in a 5-year research support program which will continue, and we have responded to that by spending millions and millions of dollars on alternative sources.

Finally, something that I am not sure you always remember, Mr. Wyden, but, we have an infrastructure investment which must generate a return to our stockholders. If we keep an investment in R&D going so that we can respond in 2 years to such a challenge as Taxol, such an extraordinary challenge as Taxol, that requires some return on investment so we can keep the infrastructure in place.

Mr. Skelton. Will the gentleman yield?

Chairman Wyden. I would be happy.

Mr. Skelton. So that I understand it, Doctor, Mr. Wyden asked what did you do besides put it into a pretty little box. You gave a list of things. Now, so I understand it, it sounds to me as if all of the items on that list go into good marketing practice as opposed to doing something for, or with, the product itself. Am I correct?

Dr. Horovitz. No; that is not correct, Mr. Skelton.

Mr. Skelton. Do me a favor and go over them——

Dr. Horovitz. Of course.

Mr. SKELTON [continuing]. Rather quickly because we don't want to take a lot of time, and tell me if each one of them is necessary for good marketing practice, please.

Dr. HOROVITZ. Let me do it in the way I think would be of more benefit to you.

Mr. SKELTON. Doctor, do what I ask. Number one, answer my question.

Dr. HOROVITZ. Yes; I will.

The things that you refer to as far as marketing are as I mentioned, only physician education. That was the only thing I mentioned that was marketing. Everything else is related to being able to supply the drug to the NCI, to obtain FDA approval, and to be able to supply it to the public, which we have now done, and to find alternative sources for making Taxol.

Mr. SKELTON. None of those are necessary for good marketing?

Dr. HOROVITZ. Those are necessary to make the drug available to the public.

Mr. SKELTON. Are any of those——

Dr. HOROVITZ. No; they are not necessary for marketing. No; they are not, sir.

Mr. SKELTON. None of those are necessary for good marketing? Is that what you are telling us?

Dr. HOROVITZ. No; they are not.

Chairman WYDEN. I thank my colleague. Mr. Skelton has been a great ally on so many issues involving the needs of the consumer and older people and others, and I want to recognize him as well in a minute.

Dr. Horovitz, just a couple of other questions, and we appreciate your patience.

Has NCI or NIH ever asked the company to share with them your cost and expenses associated with Taxol?

Dr. HOROVITZ. I don't believe so. I wasn't in all the discussions between the NCI and our company. I think most of those revolved around what is in the CRADA, and the fair pricing clause in the CRADA, and discussions of whether we were providing what we promised in the CRADA.

Chairman WYDEN. If you were asked to share that data with the National Cancer Institute or the National Institutes of Health, would you?

Dr. HOROVITZ. I think our answer would be—or maybe has already been—that that is proprietary information, and we don't believe that we can share that.

Chairman WYDEN. When determining a price for drugs that Bristol-Myers develops on its own, having nothing to do with the Federal Government, do you take into account your costs and expenses in developing, testing, manufacturing, distributing, and marketing the drug?

Dr. HOROVITZ. We take into account all those things, all the things that I had mentioned, and the fact that the marketplace will have competition, what that competition will be, what our exclusivity will be. There are hundreds of factors that have to be taken into consideration. I think, if it is a novel, unique compound like Taxol is, if it were our patented product, we would certainly try to price it at a premium, because a premium price—meaning a premium over what is on the market today—that is why we do research, to come up with something better.

Chairman WYDEN. But you have said that your private company, when you are out on your own, looks at all those questions, and I am sure that you do it very rigorously. Why shouldn't the Federal Government have a chance to do the same rigorous work in determining a fair price when Dr. Broder has said that this drug was discovered and developed, with Federal dollars, from trees harvested on Federal lands? Why shouldn't the Federal Government be in a position to do the same kinds of things when tax dollars are involved that you can do when it is just your own money?

Dr. HOROVITZ. The Government could obviously ask for that in negotiations in the CRADA, and it would be up to the private partner to decide whether they believe that could be done objectively, can be evaluated objectively, and could be kept confidential.

In this case of Taxol, there was really no patent on Taxol. Our negotiations resulted in a fair and reasonable pricing clause, and that information was not asked for in the CRADA. I think when you don't have a patent on a drug, you have limited exclusivity, then the situation is different.

Each CRADA, I believe, as I have said, should be negotiated differently. I believe I read that Professor Schondelmeyer has said the same thing, that really it is in the negotiations and the finalizations of a contract. If we make an agreement with a university or a private company, we negotiate what each partner's responsibilities are and what they get up front. That is signed. Then those partners never have any input into the pricing, if and when it finally reaches the market.

Chairman WYDEN. Well, I am excusing you at this time. But I want you to know that my sense is that we have a very, very thorny dilemma here. Unless there is a willingness on the part of the Government, drug companies, and all parties to try to better find the balance between getting drugs out quickly and making sure they are reasonably priced, a lot of our constituents are going to believe that tax dollars are being ripped off, and a lot of those drugs would have been developed anyway. We are going to have witnesses who are going to come today and raise exactly that question.

Unless this situation is remedied, it would seem to me that the technology transfer process, which I think has many great virtues and many great possibilities, would, in effect, be damaged, possibly, irreparably.

I want to find a good balance. But I will tell you, Dr. Horovitz, when a company like yours says that you aren't willing to support any kind of changes, and that you and others are just going to walk away if we insist on a reasonable pricing analysis, that doesn't strike me as a responsible contribution to this debate.

I think you will be met more than halfway. I, myself, have suggested a variety of ideas that would ensure confidentiality; your company has rejected them all. But the idea that the American people will get simply the choice of either getting sick or getting gouged, is not going to be acceptable.

People are going to want to have a better way of making sure that they can get treatments at reasonable costs than they have today. We will be asking for your input and your ideas in the days ahead.

But let me leave you with the fact that when my constituents read that Dr. Broder said that this drug was discovered and development by the Federal Government, and then they see all the things that the Federal Government did, they want to know why the price is so high. The inability of either you, Dr. Chabner, or you, Dr. Horovitz, to come before this subcommittee and say how that price was arrived at, in even the most general kind of way, contributes greatly to the problem we have in resolving a very thorny and difficult issue.

I hope that we will see constructive suggestions from NIH, which Mr. Adler tells us has no policy at all as of today, and Dr. Horovitz, who, I think, tells us essentially that we all ought to be very happy because the drug has gotten out there quickly but that the price ought to be whatever Dr. Horovitz and his associates think it ought to be. We have to do better.

My colleague, Congressman Skelton.

Mr. SKELTON. Thank you.

Chairman WYDEN. Anything you want to add further, gentlemen?

Dr. CHABNER. I would like to just say, I think it is very unfortunate that the word "gouging" is being used here. I don't think there is any evidence that there is gouging here. This price, given the difficulty of production, seems to me, a very reasonable price.

I am not an expert on drug pricing, but this company has fulfilled every aspect of this CRADA. I think it is unfortunate to brand them as "gouging."

Chairman WYDEN. Well, Dr. Chabner, I don't know if you are referring to me, but I have gone to great lengths to say that the public is way too deeply in the dark for anyone to make an assertion like that. The issue here is whether or not it is acceptable to keep the public in the dark on pricing issues when the public has done so much of the heavy lifting to get these drugs to market. That is the issue.

It may well be that the price of this drug is justified. But until we get some accurate information with respect to the costs and the potential for profit, even some very generalized kind of information, I don't see how you can come to the committee and say that the public is being treated fairly. We don't know that. That is what the issue at hand is.

Mr. Adler, further comment?

Mr. ADLER. Yes, sir.

As you know, the Federal Technology Transfer Act of 1986, which I feel is a very marvelous and very exciting statutory initiative, says nothing about Federal laboratories injecting themselves into market or traditional market activities like price setting or price determinations.

NIH is only one of the Government's 500 Federal laboratories that has raised pricing and public investment as an issue and highlighted it very conspicuously in its policies and model agreements. I think, as you have said, that there are challenges for the Federal Government in establishing a fair and appropriate policy. I appreciate very much the chance to work with you and your staff on these issues. But they are not simple issues, and moving imprudently may be ultimately to the detriment of technology transfer and the public.

Chairman WYDEN. Mr. Adler, that is a fair point, but we have got to move. We don't want to move imprudently, but we have got to move.

I think the fact that this issue with respect to technology transfer has become so controversial, as it relates to drugs and medicine, reflects the fact that health care is the biggest industry in the United States. Certainly, through the 1980's the drug companies were making extraordinary profits. Many of my constituents, very frankly, say that Government should set limits on drugs that are completely the fruit of the private sector. I have not supported that sort of thing.

But now we face the situation where it is not just the genius, creativity, and entrepreneurship of the private sector, it is, to a great extent, the Federal Government's genius, creativity, and skill in discovering and developing these drugs, and the taxpayers want some answers.

As you know, we asked to work with you all 14 months ago on these issues. I am not convinced there has been a lot of progress made in 14 months.

Very frankly, my desire is going to be with my colleagues on both sides of the aisle and the new Secretary of Health and Human Services to make sure there is a process to work with the relevant parties and work through these issues quickly. It is not going to be acceptable any longer with the Federal deficit being the way it is, and medical bills escalating the way they are, to just come on and tell us that the price of a drug like Taxol is going to be like some other arbitrarily priced drug.

We will have conversations on that, I am sure. We have disagreements, but they have always been expressed as differences among reasonable people.

We thank you for your cooperation.

We will excuse you at this time.

Chairman WYDEN. Our next panel, is Mrs. Karen Guth, Denver, Colorado, accompanied by Herb Jacobson; Ms. Abbey Meyers, executive director, The National Organization for Rare Disorders, New Fairfield, Connecticut; and Mr. James Packard Love, director, Taxpayer Assets Project.

Do we have Ms. Meyers?

I gather the three of you will all be addressing the subcommittee and answering questions.

Do any of you have any objection to being sworn as a witness? Please rise and raise your right hand.

[Witnesses sworn.]

Chairman WYDEN. Mr. Love, why don't we begin with you.

Let's pull that microphone around to you, and please begin.

TESTIMONY OF JAMES P. LOVE, DIRECTOR, TAXPAYER ASSETS PROJECT, CENTER FOR STUDY OF RESPONSIVE LAW

Mr. LOVE. Thank you very much, Mr. Chairman.

As you know, this is the second time I have appeared before this subcommittee addressing similar issues. I was a witness in the July 9, 1991, hearing, where the Taxol CRADA was discussed.

I would like to focus primarily on the issue of the pricing of Taxol but also to make some general statements about Government policy toward Government-developed drugs.

I would like to clarify some of the issues raised by some of the previous witnesses.

There has been some confusion about the price of a Taxol treatment. The price per milligram of Taxol is $4.87; that is the wholesale price. The $986 figure for the cost of a treatment which is used by Dr. Chabner and Dr. Horovitz to describe the average cost of a treatment is, according to the NCI officials who we talked to, the amount that a woman who weighed about 105 pounds would receive.

We have looked at the NCI protocols for ovarian cancer and breast cancer for which Taxol is being prescribed, even though it hasn't received FDA approval. There has been a systematic attempt to low-ball the cost of a Taxol treatment.

A cycle of treatment is an injection administered every 3 weeks. Patients responding to therapy receive about eight cycles of treatment.

The drug is sold in 30 milligram vials. According to NCI officials, eight vials is a common dose for a single treatment cycle.

For a patient using the eight vials per dose, Taxol will cost $1,169 per injection, and $9,350 for the full eight-cycle course of treatment. It is also important to recognize that the NCI protocols for Taxol require 30-percent higher doses for women with breast cancer than they do for women with ovarian cancer.

In terms of the compassionate-release program that was described, well, we will have to see how much is given away under the program. To get to the weighted-average figure that was described by Bristol-Myers, they would have to give away 20 to 30 percent of total output to compassionate-release. If you are poor enough, you can always get on Medicaid or Medicare, so I don't know who they are going to give the 20 or 30 percent too.

You are going to discuss Ceredase and other drugs, and you will hear some different stories about the compassionate-use program. There are stories about people who had to sell their homes before they could be considered qualified.

You have to look at the numbers that are available now, particularly the wholesale price. In terms of what it costs the Government to develop Taxol, in 1991 we talked to Dr. Saul Shepartz from the National Cancer Institute, and he advised us they were able to acquire Taxol for around $600 a gram. That comes out to 60-cents a milligram. Independently, we checked with firms in Colorado and elsewhere that wanted to manufacture Taxol. This is right about the time the CRADA was coming together. They told us that if we wanted to buy Taxol, that we could buy it at between 55- and 60-cents per milligram, and that was basically the going rate. Not the price charged by the drug companies, but the firms that collect the bark and manufacture Taxol.

At the time, the 60 cents per milligram was really what everyone looked at as the Government's cost.

As Bristol-Myers scales up to larger production, officials from both Bristol-Myers and NCI told us they think the 60-cent figure is going to fall; they say the result of moving from small production to larger production is not going to increase their cost per unit, but decrease it.

There is also a lot of confusion about how much or what the role of Bristol-Myers played in the development of Taxol. Bristol-Myers didn't sign the agreement until 1991. The discovery that ovarian cancer was treatable by Taxol occurred in 1988.

The Government sponsored the clinical trials. The Government sponsored the phase III trials for breast cancer and ovarian cancer. The role of Bristol-Myers was to supply the drug to the Government so the Government could use it in the clinical trials.

The company didn't run the trials. They just supplied the drug. Now, I don't know how much Taxol they provided the Government, but according to the best estimate we could make, based on Dr. Horovitz' testimony, is that they provided around 16 kilos of Taxol to NCI to date, for clinical trials and distribution. They can correct me right this minute, if that is wrong, or if it is not in the ball park. I don't think that is a highly proprietary number. Is 16 milligrams—perhaps the Chair could——

Chairman Wyden. Let us ask the questions. We will attempt to ascertain that from Bristol-Myers.

Mr. Love. If it was 16, then the cost to the Government was probably around $10 million. So, that was, I think, what you consider to be their role in the development of the drug.

Now, when I say $10 million, that would cover the manufacture and collection cost.

Now, there is a question of the so-called $114 million. Dr. Zola Horovitz appeared on the MacNeil-Lehrer Hour and referred to Taxol as the most expensive oncology project that has ever been developed. I called him up and asked, how did you guys spend so much money, when you are basically just providing the drug to the Government for its trials? He said, we haven't really spent the $100 million, but we have plans to, and a lot of it was associated with the issue of new supplies. In our discussion, he didn't break things down, but he said they include items like scaling up production. That means the cost of the plant, and I assume that not only from our discussions with him but with other people at NCI. The $114 million includes long-term contracts with Weyerhaeuser to provide yew trees, and things like that. It is expenses related to the acquiring of patents and long-term contracts to get the supply of Taxol from different kinds of vendors, private lands, not Government lands, and things like that.

Those are things that are reflected in the manufacturing cost. They don't relate to research.

Now, when we talk about the development of drugs, everyone else in the business talks about drug-development costs as the testing of the drug, the discovery of the drug—those sorts of items. So, the $114 million, except for whatever expenditures they expend on preparing the NDA application, which most people would estimate is nowhere near that amount, that is pretty much a paperwork problem, that $114 is primarily associated with things that are relating to what is going to go into the normal cost of producing the drug. I doubt if it is going to be anywhere more than the 60 cents a milligram the Government was paying.

Now, in terms of the pricing, I have a table I would like to turn to, Table 2, on page 9. This was the model that was used by NCI to determine the fair price for Taxol. Bristol-Myers was given 15 drugs. They were told to price Taxol at no more than the median of the 15. Now, the median was $1,776 for BCG; that is the price that Bristol-Myers was told it couldn't go higher than.

We wanted to figure out how you compare the price that was announced to the median price which was given to Bristol-Myers by the Government.

The dollar costs that were given to Bristol-Myers Squibb were for a month of treatment. Taxol is administered every 3 weeks. So, you use 1.44 doses of Taxol per month of Taxol.

If you take eight vials per injection and you cost that out at the $4.87, and you multiply that by 1.44, you get $1,687, which is just a few dollars less than what they were told by NCI that they couldn't go above. So, I think you will find that, in fact, NCI did set the price of Taxol. The price of Taxol is right under the $1,776.

Now you have to ask yourself, where did this list come from? Well, it is described as recently approved cancer drugs, plus cisplatin, an older drug, which Bristol-Myers sells, which is another Government-developed drug. There is another drug, human growth hormone, listed here as a drug that costs $2,500 a month. That is not a cancer drug. So, if you take another drug that is not a cancer drug instead, suppose, for example, you took ddI, which the Government just determined is fair at a price less than $2,000 a year, or less than $200 a month, and put that on this list, the medium would fall from $1,776 to $1,030. It would be a 42-percent decrease in what was considered a fair price.

In other words, by just taking the human growth hormone out and putting something like AZT or ddI in, you get a 42 percent reduction, based on their own methodology.

Now, there are all kinds of questions you can ask about this list. Why the cost of a monthly treatment? Why not, say, a completed course of treatment?

Why not the cost of a treatment over a period of a year? Why not the cost of a single injection?

There are a million ways you can slice it. There is no good reason why this is a better or worse approach than other ones. But the results are fairly arbitrary.

I would like to give you another way of looking at this list. The last drug is levamisole, to treat colon cancer. The Government spent $11 million in research which was essential in getting the new drug approval.

It is listed as $100 a month. I talked to some NCI officials and said, if you were to use this procedure with levamisole, you would have to increase the price of levamisole by a factor of 17 times to make it fair. Then if you went to the bottom of the list again, you have to crank that one up, and I don't know where you end up, but they all end up at the top.

Levamisole, the least-expensive drug, was developed and sold for many years to de-worm sheep. It cost a nickel a pill. The Government spent $11 million, proved it could treat ovarian cancer. Johnson and Johnson, who was still holding a patent on the drug, raised the price to $5 a pill, an increase of over 100 times on what they were charging the farmers to treat sheep.

So, in my mind, that demonstrated that even the lowest-priced drug on the list could be overpriced. I discussed this with Dr. Chabner, the person on the previous panel, and he said to me, that is ridiculous, levamisole is no big deal. At $100 a month, it is cheap. It is a bargain.

Now, that is the attitude at the National Cancer Institute. I mean, until you are talking about serious money, maybe the cost of a Mercedes-Benz or something like that, you are not talking about anything that anybody really cares about.

Now, not every patient has the same kind of income and health insurance policy that high officials at the National Cancer Institute and the National Institutes of Health have. For a lot of people, an extra $1,000, $2,000, or an extra $5,000 on the price of a drug is important.

The fact of the matter is the Government can produce Taxol at 60-cents a milligram. The company is selling it at $4.87 a milligram. Their probable investment in the drug, up to the point where the new drug approval was made in terms of research-related expenses, was probably between $10 and $15 million.

The day the NDA was approved for Taxol, the price of Bristol-Myers' stock rose 75-cents a share on 533-million shares, or an increase in market value in one day of $400 million. That is for an event that was widely anticipated by everyone in the investment community.

Now, I would like to turn to——

Chairman WYDEN. If you would, please highlight your principle additional concerns. That would be helpful.

Mr. LOVE. Certainly. I would like to go to the very back of my testimony where I have three figures. I will just go over the three figures very quickly.

Figure 1 is a chart which shows a relative investment by the Federal Government, the private industry, and others in health care research. As you can see, the Federal Government in 1990, according to the National Institutes of Health, paid for 42 percent of all health care research in the United States; the industry paid for 47 percent.

The role of the Government is big, so it is a big issue. There are a lot of drugs other than Taxol.

One other point: Since the Government typically invests early in the product cycle, the present value of the Government's investment is higher than the present value of the industry investment, because they typically come in further on down the pike. In fact, studies on drug pricing indicates that a dollar spent on preclinical research is worth twice a dollar spent on phase III development in terms of the present value on the dollar.

On figure 2, at the very back of the testimony, the study that most people quote in terms of the cost development of a new drug, is a study that comes up with this figure that it costs $231 million to develop a drug. We are not prepared at this point to critique the study one way or the other, but I think one of the interesting points is that they estimate that 67 percent of the cost of any drug development is in the preclinical stage, and by the time you go to phase III, you have paid for all but about 12 to 16 percent of the cost of developing the drug.

So, if a company is licensing a drug in phase II or phase III, they shouldn't be pricing it as if they did everything. It is as if the Government was to go to a farmer, plant and water their crops, and when it is ready to be harvested, allow a private company to roll their tractors in, bring it to market, and get the same in the market as everyone else does for their goods, regardless of who basically planted their crops.

Finally, in figure 3, studies of cost. I wanted to highlight four studies of the cost of the development of a new drug. The point of this graph, which shows that a study in 1972 estimated the cost of a new chemical entity to be around $22 million, a 1979 study estimated about $54 million, a 1987 study—incidentally, sponsored by the Pharmaceutical Manufacturers Association, estimated that the cost was $125 million. By 1991, the cost was estimated at $231 million.

Now, whether these numbers are too large or small, the trend is pretty clear, and that is something you have to look at. The cost of a new drug in the 1970's was probably $100. In the early 1980's, the cost was exceeding a $1,000, or $2,000 dollars. Now we are seeing drugs breaking the $100,000 barrier.

[Mr. Love's statement, with charts, may be found in the appendix.]

Chairman WYDEN. You have done an excellent job in highlighting a lot of the concerns I have had. We will have some questions in a moment.

Mrs. Guth.

TESTIMONY OF KAREN GUTH, DENVER, CO, ACCOMPANIED BY HERB JACOBSON

Mrs. GUTH. Good morning. Good afternoon.

My name is Karen Guth. I live in Denver, Colorado, with my husband and two beautiful sons.

I graduated from the Colorado College with honors. I went to complete my masters of arts in teaching, and I teach and work in a myriad of volunteer positions in my community.

I will be 35 years old in March, and I have a rare genetic disorder called Gauchers disease. This affects approximately 22,000 Americans, the majority of whom are of Eastern European Jewish decent.

Thanks to my family, I have overcome many of my handicaps. My father here, Herb Jacobson, and I have been able to become a productive and compassionate member of our society.

Today, I am here to tell about my battle against the drug company, Genzyme Corp. This is a company which used NIH research results, funded for over 35 years by our tax dollars and private donations, to create a multimillion dollar corporation at the expense of the health insurance companies, the Government-sponsored Medicaid program, and worst of all, at the expense of the emotional and financial well-being of people who are afflicted with a debilitating disease.

The Genzyme Corp. has taken the Orphan Drug Act, intended to help people in my situation, and they have interpreted it to the full extent of their greed. As you know, more and more companies will and are following in their barbarous footsteps.

Our Government gave the NIH money to discover these treatments, and now the Government is forced to pay for the drugs when the patient's health insurance runs out. Because of the gross costs of these drugs, the patients must resort to going on to Medicaid in order to obtain these life-saving medications.

The Genzyme Corp. is currently the only company manufacturing a drug which could treat my physical disease. It would cost me $350,000 a year in order to take this drug developed by Dr. Roscoe Brady at the NIH. This is just the cost of the drug, not the administration of it.

We have a family health insurance policy, but it has a lifetime cap, and once we have met that limit, my family would be left without health insurance.

The Genzyme Corp's, vice president, Mr. William Pursley, and a slew of their reimbursement specialists have called me and my doctors the past few years to implore me to take their drug with the assurance that the Genzyme's attorneys would force my health insurance company to repay and reimburse them for the cost of the drug. Genzyme Corp. is spending a fortune marketing their product, Ceredase, through magazine publications, video productions, conferences, and lavish, all-expense-paid seminars for medical professionals. I have one physician who said to me, I am going to hold out for the trip to Tahiti.

Now, you may ask, as I have asked myself, why would a drug company so aggressively market directly to patients? They do this because they know that once a person who has lived with a debilitating chronic illness starts to feel better, through dependency upon Ceredase, their drug, we will sacrifice anything and everything to continue to get our treatment. Like a junkie, we will use up our health insurance, we will quit our jobs, we will divorce our spouses so that we may declare ourselves legally indigent to receive Medicaid. All the while, companies like Genzyme are collecting unprecedented revenues.

My recommendations to the committee are as follows: I implore you to investigate the Genzyme Corp. and the NIH. Look into the contracts between the two of them. Learn the truth about how the drug, Ceredase, was developed over the last 35 years with tax dollars and private donations, from the NIH, not the Genzyme Corp. Find out how the price of Ceredase was established. We don't know why, after the NIH developed it, Genzyme has all rights and privileges to charge whatever they see fit.

Demand that Genzyme Corp. make a full disclosure of its costs for both the original Ceredase derived from human tissue, and the new biotech or recombinant product. Discover who from the NIH sold out to the Genzyme Corp. and what other Government-paid researchers are selling out to other Johnny-come-lately drug companies for a piece of these enormous-nitch, market profits.

Set a cap on the amount of profit a drug company can make on a medication under the Orphan Drug Act. After that cap is reached, allow competition to ensue in order to moderate the price and allow people to continue to receive the drug without the fear of exhausting all of our health insurance funds.

Set a fair price for an orphan drug from its onset into the marketplace. This would ensure that the drug company not only recovers its cost and makes a fair and reasonable profit—my husband and father have a business, we are all for free enterprise—but it will ensure that there will not be a demand for further Government funding for patients through Medicaid programs in order for us to continue our treatment.

The Genzyme Corp. and their cohorts at the NIH have perpetrated the worst kind of crime against humanity, one that robs people of their dignity, one that robs people of their ability to be free, independent, and productive members of a society; a crime which in the end, I believe, will rob us all of a piece of our humanity.

Today, I am here to ask you to help me speak up for the victims of their avarice. I shouldn't be here today. I should be at home with my kids, my family, taking my medicine, feeling better, with my students.

In the end, I believe that their greed will not be satiated after it destroys me. Then they will come after you and your families, and they will utterly try to destroy us all.

Thank you.

[Ms. Guth's statement may be found in the appendix.]

Chairman WYDEN. Thank you.

I am going to have some questions in a moment. But I want you to know that the reason we are holding these hearings is because we think that your tax dollars should be used to lower the price of these medicines for you, rather than on the kinds of things that you, Mr. Love, and others have pointed out, that seem to be of such, relative unimportance. This is especially of concern when a family, like you say, is about to go broke and be devastated by these costs.

The fact that someone like you will come from Colorado is going to make it easier for us to wrestle with these folks. I think you were here for the last panel. They didn't want to say much of anything because they have got a great and cozy operation right now. We are going to bust it up and stay with it until it gets done.

Mrs. GUTH. Thank you.

I wish you good luck.

Chairman WYDEN. Let me welcome Ms. Meyers, who has done lots of good work.

TESTIMONY OF ABBEY S. MEYERS, EXECUTIVE DIRECTOR, NATIONAL ORGANIZATION FOR RARE DISORDERS

Ms. ABBEY MEYERS. Thank you.

Mr. Chairman, the National Organization for Rare Disorders is a coalition of about 127 voluntary health agencies concerned about rare orphan diseases. We are the group that passed the Orphan Drug Act and have been working very hard during the last few years to try to amend it to do something about the prices of some of these extraordinary drugs.

The purpose of all of the programs that we are talking about today, the Orphan Drug Act, CRADA's, SBIR grants, and the whole gamut of Government/industry partnerships, is to encourage the commercial sector to develop drugs and treatments that would not otherwise be developed.

The idea of the Orphan Drug Act was to develop drugs that were not supposed to be profitable, and because they were money-losing drugs, the Government set up incentives to entice companies into developing them.

Let me make it very clear. We need the pharmaceutical industry to commercialize these drugs. The Government can't do it, and we can't do it. Only the pharmaceutical industry can do it.

In order to stay in business, they must make a profit. I don't know anyone who wants them to develop these drugs at cost or to give them away for free. So, they must make a profit.

Obviously, society deserves a payback. The Government has to encourage and not discourage these pharmaceutical industry partnerships with the Government. But it must protect the consumer from price gouging.

The problem is much, much bigger than Taxol. There are many programs at NIH and other Government agencies, such as the Centers for Disease Control, Department of Defense, Veterans' Administration, et cetera. CRADA's and SBIR grants are formal agreements, but most of these partnerships that we are aware of were just done by handshake; there was no guarantees on anything and no requirements.

Only CRADA's require reasonable prices. Even under the FDA's system of treatment IND's, when a manufacturer can distribute an experimental drug and the patient must pay for that drug, the FDA requires that the company can only sell the drug at cost, and yet they have no way to verify what the cost is, so they simply rubber stamp, in most cases, the manufacturer's estimates.

Neither NIH nor FDA have accountants on staff who can make these decisions. They have doctors who should not be making financial decisions in the driver's seat. We really should take a good look at that and decide where this responsibility should be placed.

Manufacturers are not required to open their books. There is not much risk for drugs that are developed with Government funds—and my written testimony includes just some of them—but the fact is practically all cancer and AIDS drugs are developed at least partially with Government funds.

The price of human growth hormone is very significant. Mr. Love mentioned it is not a cancer drug, it is a drug for children with pituitary dwarfism. The price ranges from $10,000 to $30,000 a year. It is an extraordinarily expensive drug.

AZT, when it was originally developed, costs between $8,000 and $10,000 a year. The price has gone down to $3,000 a year. I think Burroughs-Wellcome deserves a salute for that, because they were one of the few companies to ever lower their price on a drug.

Levamisole, which we just talked about, my information says it costs 6 cents a pill if you are a sheep, and $6.00 a pill if you are a human. It was developed with Government funds. The worst is Ceredase, which averages $380,000 a year.

All of these are orphan drugs. They were supposed to be subsidized by the Government because they were drugs of little commercial value. They get the Government subsidy, they get tax credits, and they get a 7-year monopoly during which they can charge any price they choose.

Even today at NIH, the Government is paying for and conducting postmarketing studies at taxpayers' expense on very profitable drugs. Human growth hormone, for example, is being studied for short children. This raises many questions, because why is NIH giving a drug to perfectly healthy children just to see if they will grow taller? So, there are ethical questions involved besides financial questions.

Why isn't the company paying for those clinical studies? Why is the taxpayer paying for it?

The Government must act to prevent further abuses, and the challenge is to determine what is a reasonable price and what is an excessive price. They should determine the valid research and development costs. They must eliminate the loopholes such as R&D partnerships which these companies set up in order to boost up their claimed expenses for research. In order to do this, somehow you should require the companies to open their books and you must keep the information confidential so that other people won't be able to find out, except for the IRS, of course.

The rest of the industrialized world does this. Other countries allow a drug to be priced only after they have examined all of these costs. Why are we so sensitive here in the United States?

You must regulate the companies like utilities. Why does the Government say you can only charge a certain amount for gas or electric? It is because people would freeze to death in the winter. It keeps them alive.

How can you say that you are not going to regulate the prices of drugs, when people's lives depend upon them?

Maybe, if the industry is right, you shouldn't do it for baldness drugs and diet pills, but when people are going to die if they don't have a drug, you have got to have some kind of control over it.

Could we ever improve the current system and design some bonuses if the Government is going to set prices for these drugs? Maybe you should come up with a formula such as the cost of R&D, the manufacturing cost, the indirect costs like we pay to universities that conduct research, profit a reasonable profit, plus a bonus for the drugs' value to society.

For example, we have a great need now in an area the companies still don't want to go near, which is development of drugs for addiction and drug abuse, and tuberculosis, which is going to be a horrible, horrible epidemic. Companies do not want to develop these drugs.

If you developed CRADA's for these drugs, you would have many companies bidding on them if you give them a bonus.

If you find that companies don't want to bid on them, or if only one company bids, give them a bonus for stepping forward to develop a drug. But when four companies step forward, as they did with Taxol, why give any of them something more than the others?

[Ms. Meyers' statement may be found in the appendix.]

Chairman WYDEN. Mrs. Meyers, thank you for an excellent presentation. If ever there was an organization that wanted to see private companies make progress and move quickly, your organization would probably be the model population.

I note at the same time, you have very strong statements to make about pricing and accountability, and I appreciate your leadership.

Let me ask a few questions of each of you.

I will start with you, Mr. Love, if I might.

I gather you are of the view that the Bristol-Myers investment, the investment that they constantly cite as being much larger than anything that the Government has made, mostly went to consolidate Bristol-Myers place in the anticancer market and to looking at analogues, similar drugs, and alternatives. Is that essentially your view?

Mr. LOVE. Well, as far as the $100 million they come up with, or $114 million, or I guess the many multiples, as expressed by Bristol-Myers, you just can't account for that in the context of the new drug approval for Taxol. The new drug approval for Taxol consists of the work that went into the discovery of the drug, the clinical testing and that sort of thing. I would think, at the maximum, their contribution to the clinical trials efforts, which is where they came in at, could have been no more than $15 million.

Now, it is conceivable that they have entered into some contracts that relate to the development of different ways of getting Taxol that could have high price tags on them. I imagine that is probably where they come up with $114 million, or whatever.

I imagine they have contracts with Weyerhaeuser and other firms maybe extending over periods of time. I think that is where the $114 million comes from.

You don't really have to have them tell you where they spent the $114 million. You can use common sense to figure out how much it costs for them to supply the drug to the trials. We know the Government could acquire it for 60 cents a gram, and they only provided 16 kilograms. The rest is just arithmetic.

Chairman WYDEN. It sounds like you are of the view that Bristol didn't spend much more than $15 to $20 million to get Taxol to market; is that correct?

Mr. LOVE. Yes; relative to what I consider the cost of going through the FDA approval. Now, once you get the approval to market, then you have to scale up, and I think they have done that for production facilities.

Now, if you want to count the cost of a plant for commercial production as an R&D expense, you can get a real high number, but most people wouldn't consider the cost of the manufacturing process the cost of developing the drug. That is the cost of producing the drug. If you are going to mix apples and oranges, you are going to put them together, you are going to get some big numbers.

I think that is the problem in the case of Ceredase. I think the company wanted to mix in the cost of the production facilities with the R&D. There are arguments that can be done to a point, but there is a point when it becomes the cost of production, not the cost of development.

Chairman WYDEN. In the case of Taxol, didn't Hauser buy the production facility and go out to the market with a stock offering?

Mr. LOVE. You probably know more about Hauser than I do, but it is a case where the Government and Bristol-Myers used the same private contractor to harvest the Taxol. I think Bristol-Myers wanted to emulate the Government by hiring private firms to do their work for them.

Chairman WYDEN. As one listens to you, one gets the impression that Bristol-Myers is claiming somebody else's investment as essentially their own, either the Government's investment or some other company's investment. We are going to continue to inquire into this question of where this $114 million that they talk about investing has gone, and anything you can do to further enlighten us in the days ahead would be helpful.

Mr. LOVE. I have discussed this with officials, both from the company, but also from NCI, and I can tell you the argument that is being made is that you have to allow them to make a lot of money on Taxol so they can use that money for development of Taxol analogues and synthetic sources; that is the crux of it.

If you buy into that, then I guess you can say that the cost of Taxol development is $114 million. If you think that is part of the cost of Taxol.

We suggest you could take that one step further. Why not allow them to make billions on Taxol and allow them to use that to develop drugs for heart disease. Where does it end?

I think that Taxol should be priced at its cost, and if they want to get money to do these other things, they should have to go to the capital markets.

Chairman WYDEN. My sense is Bristol's total unwillingness to describe where this $114 million is going certainly feeds the credibility of your argument. We are going to continue to try to excavate this information either from the company or elsewhere because I think it is central. I share your view that if taxpayer money was used to get Taxol to market, then every effort ought to be made to price Taxol reasonably because that is what the taxpayers supported. However, the taxpayers should not be in a position of giving a private company a jump to another market or solidifying a monopoly where there is real competition.

You have been helpful, and we will be anxious to work with you in the days ahead in terms of trying to flesh out further what underpins Bristol's pricing data and where this $100 million actually went.

Mr. LOVE. I hope you look at the pricing for ddI as well, because it is my understanding that they didn't get any data for ddI, and I am sure that Bristol-Myers came in fairly late to the approval process for ddI as well.

Chairman WYDEN. My sense is, and I have reviewed some of the charts, that Bristol's process for ddI is also going to raise some very interesting questions. Your point is well-taken. As you could see from this morning's experience, we are going to have our hands full trying to extricate some of this pricing data, and we will be anxious for anything that you can supply us.

Let me turn to the Coloradans for a moment.

How are you all going to be able to pay for this drug? What you have described is essentially that this price is going to be financially devastating to you and your family.

Mrs. GUTH. Well, I have a choice. I can start using up our family insurance cap, but then, of course, my family, once that is used up, will not be able to get insurance from anyplace else, and I certainly won't be able to.

I have talked to a lawyer who has said that my other option is to declare myself personally separate from my family, declare myself financially indigent, get a civil divorce, and divest myself of anything, part ownership of the house or stocks, or whatever, and go on to Medicaid.

Chairman WYDEN. Your lawyer said divorce your husband because you might have a better chance of paying for a drug that was developed with a significant amount of Government support?

Mrs. GUTH. Absolutely. That is my choice. My 7½-year-old said to me, are you going to have to divorce daddy and move out of the house? Because he is at the age where he is beginning to understand some of these issues. What do you say to him?

I mean, it is my health and I can't jeopardize his health if, God forbid, he would need health insurance, hospitalization.

So, that is the direction we are looking right now, is that I have to be prepared in order to get this drug and to stay on it—it is a treatment, not a cure—to divorce my husband and go onto Medicaid.

Chairman WYDEN. Your understanding is that this was an instance where the Federal Government essentially delivered a complete product to the manufacturer? This was one where the Federal Government basically put it on the platter and said, "here it is?"

Mrs. GUTH. Yes, the Federal Government, with private funding. I know my dad raised funds and sent them to the NIH when budgets were cut in Dr. Roscoe Brady's lab. So, there was some private funding that was raised and sent to develop this. It was developed and used at the NIH.

Then Genzyme came along, and I am not sure who gave the information to them, what kind of deal they worked out, but the pricing, of course, when it came to market, was abhorrent, to say the least.

Chairman WYDEN. So, you are being told you have to look at divorcing your husband and your father is out trying to raise money to get you treated. By the way, how did you find it possible to raise money? Does one just stand out in the corner and say, "I have to raise money for NIH?"

Mr. JACOBSON. Can I thank you for what you are doing first? Because what you are doing is a godsend. It is a very emotional issue for me.

I found out about Karen when she was about 5½. They told me to go home and forget about it. I couldn't forget about it. But I met a doctor one day and he said, Herb, don't grope for miracles.

I came home, and I got so damn mad, I said, we are going to grope for miracles. The elevator is a miracle, the telephone is a miracle.

The only thing stopping this is money. Franklin Roosevelt did it with dimes. So, I started a foundation in Denver, and we built a wing in Colorado General Hospital for research in inborn errors of metabolism.

Brady flew into town and thanked me because he said we were getting a lot of response in the Congress. We were educating a lot of people. He said, Herb, when we get this, your daughter is going to be one of the first on the list. I said, I don't want her to be the first on the list, I want everybody to get it.

A few years later he called me again and said, Mr. Nixon was cutting all the money, I am going to lose a technician we need desperately. Can you help?

So, we sent him money. We got the foundation we started. We sent him 12 postdated checks to pay for this lady so she wouldn't leave the lab.

When I met Roscoe at the foundation meeting about 2 years ago, I asked him how in the world he could do this? How could he let this price come onto the marketplace like this?

I testified before the Metzenbaum Committee last January. I was so livid with rage, I walked out after the testimony. I said to Roscoe Brady, I really in my heart feel you have abandoned all these patients. It is not enough to make a drug, but it is a cruel hoax to make a drug no one can afford.

I will tell you one factor you are not putting in here, Congressman. You are talking about——

Chairman WYDEN. I am sure there is more than one, but I want you to say it.

Mr. JACOBSON. It is a crucial one. For 30 or 35 years, you are not factoring in the hundreds of millions of dollars, the land and the equipment, the salaries, and all the other factors that are costing the taxpayers—this is a blatant example of taxpayers' taxation without representation. They have literally—we even paid for the clinical trials of Ceredase.

There are two doctors I talked to at the NIH who went to Boston almost every month on Government money because the people at Genzyme couldn't develop the technology to do this. Our Government funds did this.

I just can't imagine an 80-percent figure on a $400,000 drug—80 percent on a $5 pill. Maybe the drug companies can justify that; I am not going to get into that.

But how can you justify making 80 percent on $400,000? It is not barbaric. It is demonic to take sick and defenseless people and do this.

I know you are going to cut me off, but I have got to say something. You ought to clean out at the NIH.

I heard Mr. Adler say it is not a simple issue. It is a simple issue. I will tell you what the issue is. I used to teach history, and I love this country. There isn't any place in the universe like this; it is a beacon.

We are more than the land of the free and the home of the brave. We are the land of decency and we are always striving to restrain indecency.

Anybody who can tell me that this behavior of this drug industry is anything but indecent, it is beyond my comprehension of why we are sitting here. I have spent the last 30 years raising money, begging for this day, and then when it comes, somebody puts it under a glass and says, you can't have it unless you demean yourself, impoverish yourself.

What good is saving somebody's life to impoverish them? They ought to be ashamed of themselves.

Chairman WYDEN. I thank you for coming.

I think what you and your daughter have described is almost a textbook case of what American health care shouldn't look like.

I want you to know that this is not going to be an issue that is going to disappear in the congressional fog and get lost in a lot of blather. To me, it is unacceptable when the taxpayers and people like yourselves, who are sick, have done so much to develop these drugs, and you are just at the mercy of the companies when it comes to pricing.

I want you to know that your coming back here is not going to be in vain. We are going to be working with you and working with you closely.

Ms. Meyers, one question for you. We talked to people on Wall Street who indicated that the prospects for Taxol would be $500 to $800 million in sales per year worldwide. Based on your experience, is that a reasonable figure? Mr. Love also noted that the stock market was showing positive revitalization as well.

Ms. ABBEY MEYERS. Well, let me give credit to Bristol-Myers. They are the only company that has ever given up orphan drug designations, and they have given up two. One was for ddI for AIDS and one was for Taxol.

I certainly wish that other companies would have stepped forward and said this is not a drug of little commercial value, and it wouldn't be within the spirit and intent of the Orphan Drug Act to keep our designation. That is exactly what Bristol-Myers did.

However, the market for the drug, for Taxol, certainly is not simply ovarian cancer. It will probably work on the most prevalent cancers.

Keep in mind, there are 200 different types of cancer, approximately, and only four of them are prevalent, but they are very prevalent, and one, of course, is lung cancer, the other is breast cancer. They affect millions of people, and that is the true market for Taxol.

So, when it does get out there and the oncologists become used to using it, and when insurance companies decide they will reimbursed for it, it will have a very large market.

Chairman WYDEN. Well, you have been very patient. I gather that all of you share our view that this sort of take-it-or-leave-it approach where the drug companies just tell us it is their way or no way is unacceptable to you and you wish to request the Congress to change it, and that is what we are going to work toward on this subcommittee. We will excuse you at this time. We will be anxious to have further input from you in the days ahead. Thank you.

Our next panel, Michael E. Gluck, Office of Technology Assessment, accompanied by Dr. Alan M. Garber, U.S. Department of Veteran Affairs and assistant professor at Stanford Medical School; and also Robert F. Allnutt, executive vice president, Pharmaceutical Manufacturers Association; Steven W. Schondelmeyer, professor, College of Pharmacy, University of Minnesota; Dr. Peter Arno, Albert Einstein College of Medicine; and Ellen Stovall, executive director, National Coalition for Cancer Survivorship.

Chairman WYDEN. Gentlemen, it is the practice of this subcommittee to swear all the witnesses who come before the subcommittee. Do any of you have any objection to being sworn as a witness today?

[Witnesses sworn.]

Chairman Wyden. We are going to make your prepared remarks part of the hearing record in their entirety. I would like, because of the length of this panel, to ask each of you to try to keep your prepared remarks to 5 minutes or so. We will, as I say, make sure that your entire submission is included in the record.

Why don't we begin with you, Dr. Garber? We welcome you and Dr. Gluck. The witness table is yours.

TESTIMONY OF ALAN M. GARBER, HEALTH SERVICE RESEARCH AND DEVELOPMENT SENIOR RESEARCH ASSOCIATE, DEPARTMENT OF VETERANS AFFAIRS MEDICAL CENTER, ACCOMPANIED BY MICHAEL E. GLUCK, SENIOR ANALYST, HEALTH PROGRAM, OFFICE OF TECHNOLOGY

Dr. Garber. Thank you, Mr. Chairman.

I am with Stanford University and the Department of Veterans Affairs, and I need to say that I am speaking today at the request of the Office of Technology Assessment and as a private citizen, not representing the Department of Veterans Affairs.

I was the principal contractor for a recent Office of Technology Assessment background paper on the development of the drug Ceredase. Dr. Michael Gluck from the Office of Technology Assessment is a senior analyst in the health program and directed this background paper.

We are here today to describe the involvement of NIH in discovering and developing this drug and to comment on what this case suggests about the role of the NIH in ensuring a fair price for drugs developed with substantial Federal assistance.

Because of the previous testimony, I won't go into detail about Gaucher disease or about the drug itself, merely to point out that Ceredase is a brand name for alglucerase, an enzyme that is a promising treatment for Gaucher disease, produced by Genzyme Corp., a Massachusetts company. It is a federally designated orphan drug which entitled it to 7 years of marketing without competition from other manufacturers.

Although the development of Ceredase predated current technology transfer policies at NIH, it was very much the product of NIH research as we have heard.

NIH researchers not only identified the enzyme defect that causes Gaucher disease, they developed the method for harvesting the enzyme from human placenta and patented that; and they discovered the chemically modified form of the naturally occurring enzyme that became the commercial product, Ceredase. The NIH organized, funded, and conducted the clinical trials that were central to the FDA's approval of the drug in 1991.

Among its other investments, as we have heard, were years of research by NIH intramural researchers that was funded by a combination of private donations and Federal tax dollars. In addition, the NIH let $1 million in contracts to New England Enzyme and $9 million to Genzyme to procure a drug for various research purposes.

Although we don't know the dollar value of the intramural NIH investment, as Mr. Jacobson has stated, this investment was undoubtedly substantial.

A key point relevant to previous testimony today is that NIH's investment in this product reduced the risk that the company, Genzyme, would have to bear. It reduced the risk that the drug would prove not to be safe and effective. By identifying, synthesizing, and conducting most of the early testing of Ceredase, NIH, in effect, increased the probability that each dollar Genzyme invested would yield the return in future revenues.

We believe that Genzyme bore a risk of failure that was substantially less than that faced by the average pharmaceutical firm in deciding whether to pursue a promising R&D lead. On the basis of information that the company supplied, an OTA statement estimated that Genzyme spent $29.4 million in R&D for Ceredase during the decade leading up to its FDA approval.

Prior to approval, Genzyme received revenues under the treatment IND program of the FDA. This makes experimental treatments available for otherwise untreatable conditions, and during this period manufacturers may charge for the drug. Genzyme received revenues from patients and their insurers during this period of between $5 and $6 million dollars.

Ceredase, as we have heard, is extremely expensive, and while the total cost of the drug depends on the dosage that is administered, we estimate that per patient cost for the treatment can run from a minimum of $70,000 a year to as much as half a million dollars each year, depending on the weight of the patient and the treatment regimen administered. As we have heard, the treatment with this drug is presumed to be lifelong. This is so expensive that many patients who receive the drug will risk losing their health insurance.

In the case of Ms. Guth, in this sense, it may be more the rule than the exception, because most patients with Gaucher disease do have private insurance, and, according to data supplied by Genzyme, 73 percent of the patients receiving Ceredase in March 1992 had such insurance. Another 21 percent were covered by Medicare or Medicaid.

While Medicare itself covers only 80 percent of the cost of treatment, most Gaucher patients have supplemental private health insurance to cover the remaining 20 percent. Medicaid pays virtually all the costs associated with treatment.

The vast majority of private health insurance plans have some form of limit on lifetime benefits payable for an enrollee. We estimate that between one-third and one-half of Ceredase patients will be in a situation like that of Ms. Guth, facing the risk of exhausting their available health insurance benefits.

Genzyme does provide the drug free to patients who exhaust or otherwise lack health insurance, but they will not have insurance recovering the costs of administering the drug which is done in a physician's office or hospital, nor will they have insurance for any other medical expense that they incur for the rest of their lives, which I might add is expected to be substantial for the typical Gaucher patients. These patients would face serious obstacles to obtaining further private health insurance once they have exhausted the benefits.

You have asked us to comment on some of the policy implications of Ceredase. There is no doubt that in terms of reaching the goal of transforming NIH research into a commercial product, Ceredase is a success. However, in asking whether this project served the public interest, we must consider a broader set of issues. In particular, because most patients have health insurance policies to pay for all but a small fraction of the charges for covered drugs and other health services, they may be willing to purchase such care even when it is worth less to them than what the seller charges.

Commercial success for a health product does not mean what it does in other markets because the price is not what the consumers are paying. Insurers usually pay in turn because they have little flexibility in choosing what pharmaceuticals they cover and what prices they will pay. Virtually all private insurance contracts with prescription drug benefits agree to cover any medically indicated FDA approved pharmaceutical.

Medicaid now also pays for drugs approved by the FDA. While Medicare usually does not pay for drugs it administered on an outpatient basis, it pays for Ceredase because the drug is administered as an intravenous infusion under a physician's supervision.

If there were competing producers of this drug, it might be possible for insurers to pay for this drug at a lower cost, but Genzyme's 7-year market exclusivity awarded under the Orphan Drug Act eliminated such competition. High prices are inevitable when a profit-making firm has a monopoly on the production of the drug and when insurers must pay for it regardless of price.

When the Federal Government has transferred technology from its own laboratories to private firms, and when, as in the case of Ceredase, it pays for the drug again through public health insurance programs like Medicare and Medicaid, the Government has a responsibility to examine the price closely and perhaps act where the market itself, or insurers, cannot. This responsibility is the basis for the fair pricing clause in NIH's current licensing policies.

What lessons does a review of the cost of developing and providing Ceredase hold for any attempt by the Federal Government to analyze the fairness of prices charged for drugs that result from licensed NIH technology? The concept of fair pricing is, of course, subject to differing interpretations. It seems that the term is commonly used to mean, however, that the price charged does not greatly exceed the costs of researching, developing, manufacturing, and distributing the drug.

Our examination of this drug suggests that determining such costs is a difficult and serious task. Any attempt to analyze costs associated with drugs resulting from licensed NIH technology is likely to face challenges like those that we encountered. The capacity to conduct such an analysis will require relevant expertise. Such expertise is particularly important because this is not a routine accounting activity. There are many areas of uncertainty and controversy in estimating R&D manufacturing—and manufacturing costs. Any organization or Federal agency that attempts to conduct such analyses will need professional staff with expertise in corporate accounting and economics, among other areas.

Even though the scope of our inquiry into the costs of developing and manufacturing Ceredase was limited, we found it was important to insure input from both economists and accountants.

Implementing a fair pricing cost is not a straightforward exercise, and the implicit limits on pricing may ultimately conflict with NIH's goals of technology transfer and the collaborative development of new medicines with industry. When faced with additional scrutiny, as we have heard, some firms may opt not to license drug technology developed at NIH. The validity of this fear will only become apparent with time. But the public investment in biomedical research is substantial.

NIH research results promise to bear valuable fruits. In doing so, a concerted effort will be needed to protect the public interest. Enforcement of the NIH's fair pricing clause will require the expertise to determine the relationship between a drug's price and its cost. Such analyses may also have the added benefit of clarifying some of the broader public debate about pharmaceutical pricing and profits.

Thank you, Mr. Chairman.

[Dr. Garber's statement may be found in the appendix.]

Chairman WYDEN. Thank you, Dr. Garber.

Why don't we just go right down the line? Let's go to you next, Dr. Schondelmeyer.

TESTIMONY OF STEVEN W. SCHONDELMEYER, PROFESSOR, COLLEGE OF PHARMACY, UNIVERSITY OF MINNESOTA

Dr. SCHONDELMEYER. Again, I also thank you, Mr. Chairman, for having me here.

I come from the University of Minnesota. My experience has been in studying the pricing trends and pharmaceutical marketplace for over a decade now, and in that process I have studied pricing trends at all levels: The consumer level, the retail level, the manufacturer level, and the wholesale level.

Certainly, new therapies, as we have heard about with Taxol, are welcome and needed in the marketplace. Also, the cooperation between NIH and the industry is exciting to hear about. It is important, and we all encourage that cooperation. NIH has dealt quite admirably with the scientific and technological issues and aspects of bringing products to the market through CRADA's.

NIH, actually, in the process of reviewing this Taxol product, had requested information from Bristol-Myers Squibb to do a bit more detailed assessment, and one of the responses back from Bristol-Myers Squibb was that if we took the time to compile all of that information, it might delay the introduction of that product on the marketplace, and we would hate to do that.

The CRADA policy statement that appeared to have been in effect at the time that the Bristol-Myers-NIH CRADA was adopted had language that said, and I quote this part, "that licenses granted for NIH intellectual property rights may require that this relationship," meaning the price relationship, "be supported by reasonable evidence." So, apparently, at least the policy statement, if not the actual contract they signed, said that not only is there a relationship between price and the public value, but that it may be required to be supported by reasonable evidence.

So, there appears to have been some language that might have given Bristol-Myers a clue that Congressman Wyden and others would ask this question at some point, if it wasn't answered to NIH directly in the first place.

With this policy statement, one can then ask if this same language was not in the Taxol CRADA, why not? If it was, then why is Bristol-Myers so surprised that they are being asked to supply that reasonable evidence at this point?

I would point out here that the real issue is not the pricing of the drug per se. That is partly the way we are asking for the public to get their value back out of this product, but the real issue is the Federal Government and taxpayers, through the dollars we pass to the Federal Government, have made a substantial investment in discovering valuable intellectual property, and that valuable intellectual property is being transferred to the private marketplace for the private gain of a private corporation at virtually no cost to that private corporation.

I would like to point this out, that, actually, there are several ways then that that valuable property could be transferred and the public get back some of that value. The public, through NIH's agreement with the drug company, could either get royalties or a lump sum payment or a reasonable concession on the price of the drug product or some combination of all those once we determine a reasonable value for the product in the marketplace and the value that intellectual property might have in the future.

I am not at all saying we should double count and ask for a royalty, a lower price, and a lump sum payment, but we can determine the value of that intellectual property, then come up with a way to distribute the acquiring of that value back for the purposes of the Government and the public in general.

In fact, at the NIH advisory board meeting that I attended in December, there was serious debate about whether NIH even had the capability internally to assess a reasonable and fair price. I don't know the exact consensus, but most of the discussion I heard was that they didn't feel they had the ability to make such a judgment, yet we hear that they have decided that the Taxol price is reasonable and fair.

I would like to ask you just for a moment to imagine, if you will, that there is a company called XYZ, Inc., and XYZ, Inc., through their research scientists, have discovered a valuable new drug, and they realize that they don't have the marketing capabilities and clinical capabilities to develop that drug, so they go to a mega pharmaceutical corporation and say "such a deal we have for you." If you take this drug and develop it, we will let you have it. Can you imagine the reaction, not only of the board of directors of the XYZ Corp., but of their stockholders when they find out that this has occurred?

What we have had happen here is not XYZ Corp., but NIH Corp., a subsidiary of the U.S.A. corporation, has done the same thing. They have found valuable property. They have taken it and said, "here, you go market it. Keep the profits. Keep the change. Don't worry about giving us any reward back for the contribution we have made."

Basically, that is what we have done here. The American public should be up in arms with the NIH and with the Government for passing off, at no cost to Bristol-Myers Squibb, or very little cost, this valuable property, and then Bristol-Myers Squibb certainly has added value to that by taking it to the market. I don't deny that, but imagine for a moment, too, the gentleman from Bristol-Myers Squibb said that the product at present is priced at a premium price, and they felt that was justified because it brings substantial therapeutic value to the market, and I agree with that argument.

But he also said in response to a question posed by someone: If you had done all of the work for this product to bring it to the market, what would your price have been? Well, we would have chosen a premium price. He didn't give numbers for either of those, but they sound quite a bit the same. So, if you would have had a premium price if you did all the work and you seem to have about the same price with the Government doing a lot of the work, where is the Government and/or the purchaser getting any value back out of this process, other than the privilege of being able to buy your product on the marketplace if they can afford it or have insurance that is continuing or a Government program that is willing to write a blank check for it?

Pharmaceutical companies quite often purchase products in the marketplace on a licensed basis. They go to other companies and buy a product on a licensed basis or they go to the stores—for example I am from a university environment. Quite often a university will discover a new drug and license a pharmaceutical company to market and develop it, much like NIH has done. But always in those negotiations and agreements the university or private corporation and the drug company have a way to value the product and the intellectual property, and to negotiate a contract, and to transfer, at a reasonable price, in terms of either a lump sum or a royalty or, in this case, the Government is asking for a reasonable price in exchange for the other options. But we could choose any of those alternatives.

So, if corporations and private business, with other private corporations, can place a value on these products or in conjunction with universities can place a value on these products, why is it we can't do that with the Federal Government? Why does it suddenly become so much more difficult with NIH? How can we expect a Government body such as the NIH to act any less prudently than any other private corporation that is responsible to their stockholders?

There is no corporation that has more stockholders than the United States. The United States does have stockholders in much the same way that a private corporation does. If this is an example of the pharmaceutical industry's voluntary cooperation in helping with containing health care costs through voluntary restraint and pricing, I hate to think about what the cost and expenditures for pharmaceuticals might be if we didn't have voluntary cooperation.

The industry has often commented that they would like to let the market set a fair price, and, in most markets, that is absolutely the best way to do that. I don't blame the pharmaceutical companies for this next comment, but I would say that the market appears to be different and/or broken or not complete in the health care sector and, in particular, the pharmaceutical marketplace.

Let me put it this way. In a normal consumer market, if I am looking for color TV's, and I find one for $150 and one for $6,000, I may well decide I can afford a $150 TV, but I am not going to spend $6,000. Or I can live without either of those if that is a price I don't want to pay.

But if my wife or my daughter discovered they had breast cancer and needed Taxol, and the price of that product was more than I could afford to pay, how do I express price dissatisfaction to that pharmaceutical company? Not buy it for my daughter or my wife? That is not a very reasonable choice that I am given as a consumer to express price dissatisfaction.

I tell you that pricing decisions are much different in the health care market than they are in any other market in a free market marketplace, and I think also that, to the individual who is facing a life or death decision, the value of curing that disease that they have is almost infinite. So, the market could never place a fair or reasonable price.

My point is that, in general, the prices that are established in the marketplace for pharmaceuticals, at least the pharmaceuticals that are least price sensitive, are priced based on what we call opportunity-based pricing rather than cost-based pricing. What is the most we think we can charge that consumers can pay before it decreases our volume so much that we lose total revenue or total profitability?

One final comment. Bristol-Myers Squibb has suggested that we should look at their average weighted aggregate price rather than a list price that would be paid in the marketplace. My comment to that would be, that is fine for the drug company to look at in terms of their average cost of producing it, but if I am the individual who has to pay cash out of the pocket, it doesn't make any difference to me how much less Medicaid is paying, which by the way I pay taxes to help support in the first place. It doesn't make any difference how much less VA is paying or how much less an insurance company or an HMO pays. If I am paying cash out-of-pocket, I am paying the full price, and that is the only price that is relevant to me as a consumer at that point in time.

So, the list price is the critical price that we need to focus on in looking at what is the impact in the marketplace. I would suggest that we need some place in this Government, an organized process to monitor and evaluate appropriateness and reasonableness of pharmaceutical pricing.

I can tell you in Canada, for example, they have the Canadian Patent Medicine Prices Review Board, which by the way the Canadian Parliament is just about to pass a new law that would even strengthen the ability of that board to set and have sanctions over setting initial prices of new drugs, not to mention monitoring the price increases of old drugs.

Nearly every other industrialized country in the world has some form of price or profit control, and actually what seems to be happening in the world marketplace is that most other countries, that also pay for most all of their health care, are squeezing the balloon of pharmaceutical prices, and the bulge happens to be coming out in the United States.

I think, if for no other reason, we may need to look at some way of pushing back so that the rest of the world begins to bear some of the weight that they have responsibility for paying. I think in the United States we are willing to pay some premium for pharmaceuticals because we have a lot of the enterprise that does the research and development, but we are not willing to pay an ever-growing premium price over what the rest of the world pays for pharmaceuticals.

I would close by saying that I think we need to have somewhere in our Government a mechanism that can evaluate and provide feedback to this marketplace which doesn't seem to be working very well by itself. Thank you.

[Dr. Schondelmeyer's statement may be found in the appendix.]

Chairman WYDEN. Doctor, thank you.

Ms. Stovall, welcome. We didn't get to swear you in. I think you were out of the room. Do you have any objection to being sworn as a witness?

Ms. STOVALL. Not at all.

[Witness sworn.]

Chairman WYDEN. We welcome you. We really do have to adhere to the 5-minute limit. We are going to make your prepared remarks a part of the record. If you could take 5 minutes or so and summarize your principal concerns, that would be helpful.

TESTIMONY OF ELLEN STOVALL, EXECUTIVE DIRECTOR, THE NATIONAL COALITION FOR CANCER SURVIVORSHIP

Ms. STOVALL. Thank you very much.

My name is Ellen Stovall. I am executive director of the National Coalition for Cancer Survivorship. We are the largest national nonprofit organization advocating on behalf of people with all types of cancer. Our members include hundreds of grassroots organizations, including the National Breast Cancer Coalition, the National Alliance of Breast Cancer Organizations, Susan B. Comben Foundation, US–TOO, which is the largest men's prostate cancer support group in the country, the Candlelighters Childhood Cancer Foundation, American Cancer Society, and most of this country's leading cancer treatment institutions.

Our most important constituency, however, are the more than 8 million people in this country living today with the diagnosis of cancer, including myself. Of utmost concern to NCCS and its members is the urgently needed reform of our health care system which will allow for access to state-of-the-art cancer treatment for all Americans.

Based on health status alone, people with cancer experience discrimination and are largely denied access to coverage under the guise of preexisting conditions. This unacceptable practice must be eliminated by any reform of our health care system, and NCCS recognizes a responsibility to approach this reform with measures that address the inevitable cost containment components, many of which are being discussed here today.

We are concerned, however, with any regulations or reforms toward cost containment that would fail to acknowledge the necessity for comprehensive, high-quality cancer services. Like people with AIDS and other chronic and life-threatening illnesses, people living with a cancer diagnosis frequently must face the fact that there is no known cure for their illness. Until more is known about the prevention and control of cancer, our greatest hope lies in the discovery and development of new anticancer agents.

Our collective efforts toward expanded availability to health care are futile if we cannot offer our citizens access to the most advanced medical technology in the world. We heartily endorse any initiative, public, private, or collaborative, that will increase the prospects for cancer survival.

NCCS appreciates this committee's interest regarding the fair pricing clauses of drugs developed under CRADA's. We commend it for its efforts to act in the public interest to ensure that collaborators in these agreements perform responsibly. As you know, CRADA's offer one of the most promising mechanisms for the public and private sector to cooperate in bringing new drugs to market, and we urge you to do everything you can to assure that this cooperative agreement can thrive.

NCCS currently does not support or discourage the use or promotion of any particular cancer treatment. Moreover, we are not experts in the regulatory process which sets these standards and pricing for drug development. We feel very strongly, however, that when the world's preeminent cancer research institution, the NCI, lauds the new therapy, Taxol, as the most important one developed in the last decade and that the process by which it has come to market may be jeopardized by politicizing the pricing practices, we must speak up.

You requested us to address whether restrictive pricing enforcement might discourage collaboration between the Government and private sector. We feel strongly that it would, and we could not support any regulations, pricing or otherwise, that create disincentives of any kind to industry in cooperative development of new agents discovered through federally funded research.

Furthermore, we have been very involved in working with other coalitions to increase funding for cancer research, and through that process we have become painfully aware of the lack of adequate NIH funding to carry forth the promising basic research that will result in new treatments for cancer. We are very concerned that to burden the Institute with laborious and detailed pricing evaluations would result in taking away valuable time and resources from what we feel should be its main emphasis—the precipitous development of new products that will add measurable quality to the lives of people living with this devastating illness that will strike one in three Americans and kill one in four.

We know you, particularly, Congressman Wyden, have been very supportive of very important legislation that affects the health and well-being of the American people. You and your colleagues in Congress can make a real difference for all of us living with this diagnosis by encouraging the development of new products and by fashioning a health care delivery and reimbursement system that provides for universal access to that system.

My cousin, Sally Roos Schneck, sitting behind me, is living with a diagnosis of ovarian cancer and is alive today only because of Taxol. She has traveled a long distance with me to witness these proceedings. She wrote you last week, and I ask that you might consider allowing her to say a few words before the committee.

Chairman WYDEN. Were you interested in her doing that now?

Ms. STOVALL. Any time you would like.

Chairman WYDEN. Why don't you finish, and we will hear from our other witnesses, and let me have the staff visit with your cousin. We are sort of short on time, but let's have the staff talk with her, and if she would like to speak for a few minutes, we can work that out.

Ms. STOVALL. Thank you very much.

Chairman WYDEN. All right. Does that conclude your statement?

Ms. STOVALL. It does.

[Ms. Stovall's statement, with attachment, may be found in the appendix.]

Chairman WYDEN. OK, very good.

Dr. Arno, welcome.

TESTIMONY OF PETER S. ARNO, ASSOCIATE PROFESSOR, DEPARTMENT OF EPIDEMIOLOGY AND SOCIAL MEDICINE, MONTEFIORE MEDICAL CENTER/ALBERT EINSTEIN COLLEGE OF MEDICINE

Dr. ARNO. Good morning, Mr. Chairman.

My name is Peter Arno, and I am a health economist and associate professor in the Department of Epidemiology and Social Medicine at Montefiore Medical Center and Albert Einstein College of Medicine in the Bronx. It is a privilege to be here today.

As health care reform moves to the top of the national agenda, this subcommittee is taking a bold step in examining the pricing practices of the drug industry. In my mind, your mission will best be served by seeking answers to two crucial questions. First, what is the fairest way to commercialize therapies when the Government has played a major role in their research and development? Second, what is the best way to insure that any pharmaceutical product is reasonably priced?

The "reasonable pricing" clause now included in a couple of CRADA's with private industry is a modest first attempt at injecting oversight into the marketing process.

The background to this clause is worth noting. You may recall that National Cancer Institute scientists and Federal funding played pivotal roles in the development of AZT as a treatment against AIDS. The Government then granted double monopoly protection to the Burroughs Wellcome Co. in the form of exclusive marketing rights, both under the Orphan Drug Act and from the U.S. Patent and Trademark Office. Because of this, the Government had no means of asserting control over the outrageous price the company promptly slapped on the drug.

For that, the Government has paid dearly. Millions of dollars have been diverted from the Medicaid and Ryan White Programs over the past 5 years to subsidize the cost of AZT for those who could not otherwise afford it.

To prevent that debacle from recurring, officials at NCI began to insist that a reasonable pricing clause be inserted into exclusive licensing agreements for drugs developed in public-private partnerships. Unfortunately, the terms in these CRADA contracts are vague and may be unenforceable.

It is apparent to many observers that the reasonable pricing clause needs more teeth. In order to establish a fair price for a pharmaceutical product that has been developed jointly by the Government and the private sector, much stricter standards must be established. This requires the company to disclose, in confidence, information that is currently considered proprietary. At a minimum, this should include the following data: Development cost, marketing and distribution expenses, the presence and prices of similar competing therapies, the likelihood and timing of market entry for additional competing products, the development time it will take to recover development costs, and the profit margin that has been built into the price structure.

Purportedly for competitive reasons, the drug industry is extremely reluctant to sketch this financial picture. However, an agency of the Federal Government with economic and accounting experience could appropriately collect and analyze this data in a confidential fashion. The National Institutes of Health is certainly capable of assembling the expertise needed to perform these functions, but the assignment would go beyond the purview of its scientific mission. The Health Care Financing Administration may be a more suitable agency for the task.

Would these disclosure requirements be so onerous that drug companies would choose not to participate? Some may opt out. However, it is unlikely that all companies would refuse to participate in CRADA's despite what a chorus from industry and their lobbyists might now say. Given the vast amount of basic and applied biomedical research conducted by the Federal Government and the intensely competitive international pharmaceutical marketplace, there should be no shortage of companies that are willing to collaborate with the Government.

Let me now turn briefly to a somewhat bolder approach to the control of drug pricing. If the Government, at taxpayers' expense, has contributed significantly to the development of a new drug, why confer a monopoly on a private company at all? Whether it is done through the mechanism of an exclusive licensing agreement or with a patent, the economic rationale seems slender indeed. Nor is a monopoly necessarily in the public interest.

Three strong arguments can be made against a Government granted monopoly.

First, in economic terms, the monopoly price is, by definition, higher than a competitive market price. That means that scarce resources are misallocated and consumers are held hostage to the marketing and distribution plans of a single corporation.

Second, the likelihood that insurance coverage for pharmaceuticals would be broadened in the near future means that monopoly pricing will take income away from consumers and taxpayers in the form of inflated insurance premiums and higher taxes and redistributed to the pharmaceutical industry.

Finally, the use of public funds gives the Government a moral obligation to insure that products are justly priced and that they are accessible.

By suspending the rules of competition, the current system of exclusive licensing or patent protection interferes with this mandate. At present, pharmaceutical companies are not regulated like other Government monopolies, such as the public utilities. If the industry wants to operate in a competitive marketplace, then it should live by competitive principles. That means stripping away the artificial protection of Government granted monopolies.

If it cannot or will not abide by competitive principles, then the public interest demands that its monopolies be regulated. Industry cannot be permitted to have it both ways.

I would argue that the Federal Government should grant private industry a monopoly only under two circumstances. One, if it can be demonstrated that the monopoly pricing of profits are needed to offset an extraordinary investment that was required to bring a new drug to market or, two, if the potential market for the drug is so small that no company is willing or able to invest the requisite resources in its research and development.

Under all other circumstances, the Government should grant nonexclusive licensing agreements when it has been substantially involved in the development of a new drug. The resulting competition makes a lower drug price far more likely.

Neither of these conditions prevailed in the case of Taxol or a long list of other drugs, including AZT, pentamidine, foscarnet, erythropoietin, human growth hormone, and many others.

For the past 10 years, our society has been trying to come to grips with containing health care costs. Now it has become an imperative. Two independent commissions have been chartered to advise Congress on how to contain expenditures in the two largest segments of the health care markets. The Prospective Payment Assessment Commission has been impaneled to review hospital costs and the Physician Payment Review Commission is studying the price and value of physician services. Yet the fastest growing component of health care costs, pharmaceuticals, remains exempt from administrative oversight.

In most industrialized countries of the world, some form of control over drug prices is automatic. We ought to do no less for American citizens. It is long past time to make this issue a central part in the dialogue about health care reform.

Would this sound the death knell for innovation in the pharmaceutical industry? The answer is clearly no. To understand why, we must question, at least, two assumptions that the pharmaceutical industry has ingrained in the public consciousness.

First, in endless advertising and lobbying campaigns, the industry claims that its innovative accomplishments are unsurpassed, yet between 1985 and 1990 more than 80 percent of all new FDA approved molecular entities showed only modest or little therapeutic gains over drugs that were already on the market.

Second, the industry is quick to claim that its substantial investment in research and development adequately justifies the high and rising cost of drugs, yet it remains silent when asked to document the exact nature of its expenditures or to explain why more money is spent on marketing and advertising than on R&D.

In conclusion, let me reiterate two key points. The reasonable pricing clause inserted in CRADA's will have little meaning unless the drug industry is mandated to disclose actual costs and projected profits. However, a more simple and effective approach to price controls is the elimination, under most circumstances, of Government-granted monopolies. Given the constraints of a free enterprise system, competition should be allowed to reign unless there is a good cause to take another approach.

Finally, I would like to commend this subcommittee for its willingness to take on the tough issue of pricing practices of the drug industry. Your efforts to transform the process of technology transfer so that it better serves the public interest, are sorely needed and warmly welcomed. Hopefully, these issues will remain on the table as Congress and the new administration pursue systemic reforms in the health care system during the coming months.

Thank you.

[Dr. Arno's statement may be found in the appendix.]

Chairman WYDEN. Doctor, we thank you, and we will have some questions in a moment.

Mr. Allnutt, welcome. You have been very patient through a long morning, and we will make your prepared remarks a part of the record in their entirety. If you could take 5 minutes or so, that would be helpful.

TESTIMONY OF ROBERT F. ALLNUTT, EXECUTIVE VICE PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Mr. ALLNUTT. Thank you, Mr. Chairman. I appreciate your letting me go last. I will respond in 4½ minutes to everything that has been said this morning.

Chairman WYDEN. 4½ minutes for a perfect solution so that drugs are in peoples' hands quickly and they are fairly priced will be greatly appreciated.

Mr. ALLNUTT. That is right. I will summarize, Mr. Chairman.

Over 90 percent of the new medicines brought into use in the United States are discovered, tested, developed, and produced by the private sector. But, from time to time, a number of important new therapeutic approaches are discovered by an NIH scientist, under NIH grants or through collaborative efforts with private sector scientists.

For many years, NIH has encouraged the research and eventual marketing of promising new therapies first discovered in NIH R&D by relying on the cooperation and proven capabilities of research-based pharmaceutical companies. In the Stevenson-Wydler Act of 1980 and again in the Bayh-Dole Act of 1896, Congress reaffirmed this reliance by authorizing exclusive patent license arrangements with the private sector and by authorizing Federal entities to enter into CRADA's with industrial organizations.

The 1986 act recognizes that exclusivity is a powerful incentive to private investment in the research and development necessary for the results of Government research to reach patients as new products. We believe that, in general, the 1986 act is working quite well, as are NIH's licensing and contractual policies, consistent with that act and with the Stevenson-Wydler Act.

CRADA's generally focus on early research activities such as screening compounds, developing receptor technology, and conducting other drug discovery activities. At this early stage, Government and corporate researchers can collaborate to identify and pursue research leads.

Normally, this is not the role of the Government. It is not the role of the Government to develop a compound that results from this collaboration into a commercial product. That development activity includes toxicology testing and all the other steps you have heard testified to today. These usually are the responsibility of the corporate partner.

Under NIH policy, the Government is usually compensated for its role in the early research on patented drugs by a royalty. The amount of a negotiated royalty is based on a number of factors, including the degree of risk assumed by the corporate partner. Dr. Schondelmeyer has suggested that as a solution. You have testimony here from the Industries Biotechnology Association talking about royalties as a possible solution to the conundrum you seem faced with.

Obviously, the risk of successfully completing all of these steps following discovery of a potential new therapeutic is very high. The goal of Government licensing and research policies, obviously, must be to encourage the participation of private entities, if product-specific discoveries which sometimes emerge from that research are to be developed into new therapies for patients. If these policies fail, for whatever reason, to achieve this goal, potential therapies will not be commercialized as quickly as possible or perhaps will never be made widely available to treat disease.

Included in my prepared testimony is a list of questions which the then President-elect Clinton's transition team gave us on this subject and answers that we provided them in December and also the questions provided us by the subcommittee and answers to these questions. I won't repeat all of that material at this point.

We do not believe that NIH should be in the price regulation business, and we would oppose the establishment of additional price assessment capabilities within NIH as unnecessary and counterproductive. The overriding Government goal should be to encourage companies to enter into cooperative agreements to bring promising new compounds to patients. This objective could clearly be compromised if the Government becomes more involved in reviewing, second guessing, or challenging pricing determinations for individual products.

Additional Government involvement in pricing would not only be unwise public policy but also a misuse of limited NIH research resources. As Dr. Garber testified just a few moments ago, pricing decisions are far more complex than simply reviewing development cost data, itself a complex task, and we do not view creation of the panel and process suggested in the subcommittee questions to be appropriate or necessary.

Several PMA companies are CRADA collaborators. NIH representatives testified today, and have testified earlier, that other research-based companies have declined to enter into CRADA's because of the pricing provisions or with concerns over the pricing clauses in their present state. Successful companies are not limited in their future R&D investment choices to a single product or family of therapies. A particular company, in determining how best to invest its R&D dollars, may well choose to put its resources into projects that do not raise the probability of Government agency access to internal pricing information and protracted public proceedings about pricing decisions.

That concludes my prepared testimony, Mr. Chairman. If I am still within my 5 minutes, let me just——

Chairman WYDEN. You have been such an exemplar of brevity, we will just let you go ahead and make another observation.

Mr. ALLNUTT. Mr. Chairman, 30 or 45 seconds.

I do want to respond to some of the testimony by the immediately preceding witness, Dr. Arno, where he questions the need for exclusivity where available to encourage private sector development of public sector inventions.

There is a history that goes back at least to the early 1960's of studies of that question that were good enough to convince Attorney General Kennedy's antitrust division that exclusivity was needed under such inventions, and since the early 1960's some agencies—and I happen to have been in the one that first started it—have been using exclusivity as a way to get thousands of Government inventions that were patented and sitting on the shelves into use.

So, exclusivity is very important, and I would urge you to keep that in mind as your deliberations continue.

[Mr. Allnutt's statement may be found in the appendix.]

Chairman WYDEN. Mr. Allnutt, thank you, and we will have some questions in a moment.

I share your view that there can be great rewards from the concept of exclusivity. But I hope that you all at the Pharmaceutical Manufacturers Association understand that in my view, and I think a growing number of my colleagues will tell you, that that kind of exclusivity, particularly where the Federal Government has contributed mightily in the research area, ups the ante in terms of what the private partner is going to have to do in terms of cost justification. We will have some more discussion about that here in a moment.

Now, Ms. Stovall has asked that her cousin, Sally Roos Schneck, from Chappaqua, New York, be allowed to testify. Bill Clinton has made it real clear that people are going to take back the Government, so we are going to let Ms. Sally Roos Schneck come forward, and we are going to have to swear her in and get her a chair.

Ms. Schneck, it is the practice of our subcommittee to swear all the witnesses who come before it. Do you have any objection to being sworn?

Ms. SCHNECK. No.

[Witness sworn.]

Chairman WYDEN. We welcome you. Do you have a written statement?

Ms. SCHNECK. I did write you a letter last week, my first fax ever. I would appreciate that being entered into the record.

Chairman WYDEN. We will do that. We will make that a part of the record.

[Ms. Schneck's letter may be found in the appendix.]

Chairman WYDEN. Why don't you take about 5 minutes or so and just give us your oral views?

TESTIMONY OF SALLY ROOS SCHNECK

Ms. SCHNECK. Thank you very much.

What concerns me is that women like me worried through the hassles over the spotted owl and the Pacific yew tree. But Taxol seems to keep coming under attack. For the 12,000 women with ovarian cancer who will die this year, the 12,000 who died last year, the 12,000 who will die next year, I am wondering whether you have the correct drug when you are looking into fair pricing.

Taxol was first isolated—the concentrate was first isolated in 1963. Not much happened, despite the researchers repeated requests and statements saying the drug had tremendous potential. Research just sort of lumped along. Nobody paid an awful lot of attention.

In August 1991, there were three phase II trials on women with recurrent ovarian cancer. A total of 122 women had been treated with Taxol. In approximately September 1991, through this CRADA, 1,500 women—I believe my figures are correct—received Taxol or started the protocol at 39 cancer treatment centers around the country.

The Government may have developed the drug. Nothing ever happened with it. Of the women I met in the recent phase II study, not too many of us are around any more. Most of the ones who are still alive are not in great shape. We look like every woman in this building. We look like your wives, your sisters, your daughters, your mothers. There is nothing visible that sets us apart. But I won't buy a year-long magazine subscription anymore because I am afraid I am not going to live to get my moneys' worth.

Ours is not a rare disease. So many of us are going to die of this, Taxol really is our only hope. It had much better results than any other drug developed thus far. There is no cure for ovarian cancer. But at least we can buy a little bit more time.

If you want to look into fair pricing, isn't there something that doesn't affect people's lives, hopes, a drug that has been put together quickly and marketed? This was not put together quickly. It is only within the past 2 years, as far as I can see—and I have no affiliation with any drug company—but if it hadn't been for this CRADA, I would be dead just as most of my friends with ovarian are.

Thank you.

Chairman WYDEN. Well, thank you, ma'am, and thank you for coming. I am glad that you have testified.

Chairman WYDEN. In a way I think it is really very fitting that you would be the last witness. I will tell you that it is precisely because we care so much about women's health, and particularly its future, given the skyrocketing medical prices, that we have chosen Taxol as a special case study. I would tell you that throughout this—and we began our effort before these CRADA's were even entered into—we made it very clear that we were not in any way going to do anything to lengthen the time it would take for people to get this drug.

In spite of the very serious questions we have had about environmental issues, pricing issues and the like, we have said "full steam ahead" in terms of getting this drug to people just as quickly as possible.

Ms. SCHNECK. Why would somebody go into research unless they could make a profit, too?

Chairman WYDEN. Well, we are not sure what they are making a profit on. We are not sure how much profit they are making, and we have other obligations as well, particularly since taxpayers paid for so much of the drug.

Some are charging that essentially an unfair benefit was conferred on Bristol-Myers and that others might have been able to do this just as quickly.

We are not making those charges. What we are trying to do is get some decent information from a company and a Government agency that, in our view, has essentially said, look, because people are sick, you have just got to back off and let us do what we want. I know that reasonable people differ.

I am very pleased you are here and your family is here. We just want you to know that it is precisely because we care so much about women's health and are of the view that the future of women's health will be greatly affected by pricing decisions, we are grappling with these matters. We look forward to working with you and having your input.

Ms. SCHNECK. Will you review the 99 CRADA's, also, as far as pricing?

Chairman WYDEN. We have reviewed a number of them, and, certainly, based on what the witnesses have said today, a lot of the other CRADA's have been at least as arbitrary in terms of the pricing. I do not think that because other CRADA's are arbitrary, we ought to just continue the arbitrary pricing process from now until infinity.

But I want you to know we appreciate your input. We wish to come up with a Government policy that gets drugs to people quick, makes it just as expeditious as possible, and also ensures fair pricing..

That is what we are going to be grappling with, and you and your family can help us in that regard.

Let's go back to the end of the line.

Dr. Garber, and your associate, Dr. Gluck, you all have spent a lot of time looking at the Ceredase case which we heard about. I gather that the president of Genzyme at one point said that the company was trying to find a cash cow; is that correct?

Is that a statement you are familiar with?

Dr. GARBER. It may have appeared in a Business Week article, perhaps. I don't recall that exact wording.

Chairman WYDEN. What, if anything, did NIH get out of this deal?

Dr. GLUCK. In the course of the R&D process, NIH contracted with Genzyme Corp.. In return for approximately, $10 million, over a number of years, NIH received from Gerzyne and New England

Enzyne Center the drug with which to work in their laboratories, and then in clinical trials.

Chairman WYDEN. That is what NIH got?

Dr. GLUCK. Yes.

Chairman WYDEN. What did the company get out of the deal?

Dr. GARBER. Let me comment, Mr. Chairman, that I am speaking not as a representative of the OTA now, nor as a representative of the VA. The company received a valuable service, in essence, in that much of the NIH funds were undoubtedly spent for the drug, which was in turn used for clinical trial, some of which went for approval of the drug, and some of which may have been of assistance in enabling the company to develop future dosing guidelines and perhaps even to establish some demand for the drug.

Dr. GLUCK. Also, the benefit to the company could be characterized in terms of the risk that the Federal Government absorbed, the risk that you would normally expect a pharmaceutical company entering into the R&D process to take, the risk that the drug is not going to prove safe and effective. In this case, the company had the opportunity of developing, manufacturing, and taking to the FDA a drug, much of whose effectiveness and safety had been established by the Federal Government.

Chairman WYDEN. Basically, the Federal Government shouldered the real risk, in your opinion, Dr. Gluck, for the drug's development?

Dr. GLUCK. Yes.

Chairman WYDEN. The price sounds awfully high. We heard about one family essentially getting flattened by the price of the drug, and relatives having to go out and try to raise money, and lawyers advising them to get divorced. It sounds like a real horror story kind of scenario for one family as it relates to paying for a drug, where not only has the Government done the heavy lifting, Mr. Gluck says they basically took all the risk.

Has the company ever indicated what their costs were in their relationship to the price of the final product?

Dr. GLUCK. We met with Genzyme in Cambridge last March, and they did provide us data that they termed to be confidential. It was more detailed than what you would see in a publicly available financial statement for the corporation, that is, it provided some cost data for expenditures specifically attributable to Ceredase.

We were able with that to make certain conclusions about what was R&D, and what represented other categories of expenditures, although all of this data was provided at a very aggregate level.

Ultimately, we had to depend on the presentation they made to us, that what they said was R&D for this drug was indeed R&D. We had no ability to go behind those numbers to determine in any independent way what they were spending the money on.

Chairman WYDEN. In the case of Ceredase, as well as Taxol, of course, we are struck by the whole mystery about the question of how drugs are priced and the costs involved. What does your study of Ceredase tell you about the way drugs are priced when there is significant governmental support?

Dr. GARBER. I think some of the other witnesses today, perhaps Dr. Schondelmeyer, said that in some cases it appears as though the pricing decision was made on the basis of criteria that seemed to assume there was no Government investment.

I don't know the thinking of the officials at Genzyme who set the price. But I think it is important to understand what the consequences of their pricing policy were.

Genzyme charged a very high price by any criterion. Its cost of production for this product may have been relatively high. We believe that they were. But nevertheless, we believe that their margin, and I am not speaking for OTA now, but as someone who has looked at some of the data, were quite comfortable. Their pricing policy is as follows: They charge a full price of $3.55 a unit to insured patients or their health insurers, and when they have exhausted their benefits, the drug is made available free of charge.

That is very similar to just saying, give me the remaining value of your health insurance, and I will provide you with drug for the rest of your life for free. You go figure out a way to get insurance to cover the cost of administration, which, I might add, are substantial, on the order of, perhaps, $10,000 a year. That assumes no other costs other than the charges for the intravenous infusion.

So, I don't know exactly how they set the price, but I do believe that the consequences suggest that they were trying to charge what the market would bear.

Chairman WYDEN. Well, I think we know the market bears anything when people are desperately ill. What is so tragic is that people who are desperately ill are being held politically hostage in this way, because if they don't support the status quo, then, the drug companies say, "OK, sick people are going to stay sick."

My question is, how do you now see the Congress, this committee, effectively protecting the public investment here?

Dr. GARBER. Well, Mr. Chairman, I think that is an extremely important and somewhat difficult question, because as at least two other witnesses have stated we have a model of publicly regulated utilities. We are not talking about a competitive market for drugs.

On the demand side, we have patients who are covered by health insurance. On supplying the drugs, we have a Government-created monopoly, either through regulatory provisions of the Orphan Drug Act or through patent provisions.

How should the Government best proceed? There is vast economic literature on how to proceed with regulating public monopolies. The answer typically is that if the Government played a strong role in making it possible for this monopoly to exist, the price of the product should ordinarily be low. It should be kept close to the cost of manufacturing the drug.

Dr. Schondelmeyer mentioned a couple of options for pricing. One is for the Government to share in the profits for helping this monopoly be established. That is another solution. But in most cases, we would prefer to make the drug more accessible by keeping the price relatively low.

By stating this, I don't mean to imply there are no challenges, and I think the industry representatives are quite correct that you are opening up a very complicated situation subjecting pharmaceutical companies to scrutiny to which they have not been accustomed. But at some point, we have to say, shouldn't the Government get something in return in exchange for performing this valuable research, shouldn't there be something in it for the American people other than the ability to buy a drug at a very, very high price?

Chairman WYDEN. Doctor, are you of the view that in these kinds of instances where there are CRADA's and significant Government investment, that there should be some kind of public utility kind of model?

One of the issues I am grappling with, and Mr. Allnutt touched on this when he talked about exclusivity, is I am prepared when somebody is out in the private sector and it is their genius, their creativity, their entrepreneurship that produces blockbuster products and services, to say the national free market is working and the free market ought to be allowed to have at it.

What has always been most troubling to me are these kinds of instances where it seems that the sweat and the toil of so many citizens, people who are very often sick and need to pay for these drugs, is not somehow better acknowledged. I wonder if OTA, the agency, or yourself, now advocates some kind of public utility model on pricing where it comes to CRADA's with significant Government support?

Dr. GARBER. Well, I have to tell you I most certainly will not speak for OTA in response to your question. I think the answer is that is a reasonable starting point.

The NIH has an extremely valuable stake in the intellectual property that it has developed. Yet we have heard today that they have very little idea about the additional cost required to bring a product to market. They presumably have no idea of the market value of the work that they have performed. That is, what it would have cost a private company to do what they did at the point of engaging in a CRADA or any other kind of cooperative agreement with industry.

They have to figure out things like what is the product worth, what does it cost to bring it to market, and that is very much in the vein of the public utility setup.

While I don't want to specifically endorse the public utility setup, what is needed in order to regulate a public utility is a great deal of expertise and knowledge about what it costs to produce the product. That is what the NIH or some other Federal agency will presumably need in order to effectively carry out its role.

Mr. ALLNUTT. Can I jump in, Mr. Chairman? I don't want to sound like Ross Perot when I say that.

Chairman WYDEN. Get under the hood and fix this.

Mr. ALLNUTT. We have had a lot of talk today about incentives involved in CRADA's and disincentives against being in them. If the price of getting into a CRADA with the NIH on a product were for a company to be like a public utility, I think it is clear that—I can never say never, but I can't imagine a private-sector company saying, well, we have decided to become a utility so we can work on this one drug.

It seems to me that is kind of going beyond the pale. That is why better solutions as have been mentioned here today, that relate to royalty payments, that were suggested, for example, in the questions that we got from the President-elect Clinton transition team. We said that the industry would be happy to work with NIH and others to look at ways to structure royalty systems, and so forth. That is to me a much more reasonable approach to a problem than to say we are going to restructure a company, make it become a public utility, or make it spin off a separate corporation, as a utility, in order to participate. That to me is setting up too high a hurdle.

Chairman WYDEN. So, of all the ideas that are out there on the table right now, PMA feels most comfortable with looking at a royalty type of arrangement? I happen to think that is something that ought to be considered.

Mr. ALLNUTT. The Industrial Biotechnology Association in its submission to you, which represents a number of companies that we don't. We only represent companies on the market. IBA represents a number of companies not yet on the market. They urge that very strongly.

Chairman WYDEN. Now, Bristol-Myers Squibb, to its credit, is helping the indigent, and we are pleased that they are. The typical patient, however, is going to be paying close to $1,000 for 3 weeks, for a product that Dr. Broder has said was discovered and developed by the taxpayer.

How does a royalty arrangement, in your view, and this is just conceptually, translate into something that would ensure fairness for the 85 percent, or whatever, who are probably going to have access to some kind of insurance and the like?

Would the royalty be paid to Medicare or Medicaid, or some kind of national board; how would that work?

Mr. ALLNUTT. I haven't got beyond the thought of royalty itself. Normally the royalty would be paid to the agency that is the inventing agency. Where the money goes within the Government then is another subject usually ruled upon by OMB and not the agency that gets the money, as you know.

So, it could be done in any one of a number of ways. NIH charges royalties or has royalty provisions in some of its licenses now, not all, but it is authorized under the law to have such provisions.

Chairman WYDEN. Let me project my concern, though, for you. Royalty arrangements could be an incentive for higher prices, with the possibility that people must pay more so that Government agencies get their royalties.

I would be interested in seeing a policy paper from the PMA on how a royalty arrangement could translate into price relief for the consumer. Let me just make that invitation to you, because my concern is that depending on how it was done, royalty arrangements could possibly almost create an incentive to bump the prices still higher, with the theory being that maybe down the road somebody sends a royalty check somewhere.

So, you have an invitation. We would like to explore that and any other suggestions PMA has. But we are concerned about the impact of royalties on those 85 percent of the consumers who are going to be paying $1,000 for 3 weeks of Taxol and some of these other drugs as well.

Dr. Schondelmeyer, are you concerned? Should the Congress be concerned based on what you now know, that Bristol-Myers is getting a substantial head start over its competitors in terms of marketing the next generation of Taxol analogues and related products?

I have tried to extricate some kind of information about costs from the NIH and from Bristol-Myers, and they are obviously not saying how much.

Do you think that Congress and the American people ought to be concerned that Bristol is getting a substantial head start over its competitors in marketing the next generation of these drugs, and that taxpayers essentially are giving them that boost?

Mr. SCHONDELMEYER. In one sense, we should be glad they are doing that, because their products are out there. But in the other sense, they keep telling us there is no market exclusivity in this contract; but, functionally, there will be market exclusivity. We know from other therapeutic categories that the first product in the market, if there aren't major differences among analogues, often has a substantial boost in the market. Even though it may go off patent or have challenges from competing products later on, the first product in the marketplace has a substantial advantage.

We have been talking about Government as discoverer in capturing back the value of what the Government has created in terms of valuable intellectual property. But I think there is a balance side to that, too, and that is Government as payor for health care.

I haven't done a careful cost estimate, but with crude estimates, I would guess 35 to 40 percent of Taxol will be paid for by Medicare and Medicaid. A substantial share of this product then will be paid for out of Government coffers at these, quote, "fair and reasonable prices."

So, even if we establish royalty agreements to take care of paying back the Government for the intellectual property on the NIH side, I think there may be a need for some level of body to examine reasonableness of pricing of this and other products like it for Government as a payor.

They had the same question about Ceredase; they had the same question about EPO. Other major new therapies coming along at astronomical prices need to be examined by the Government in some systematic way to determine an appropriate and reasonable price for those products in the marketplace and what the Government should pay.

Chairman WYDEN. How could you do such a thing and still be responsive to the point that Ms. Stovall and her cousin make, which I think is very compelling, and get this job done fast? That is the main thing that people look at this process and say it is a plus, it is done fast. Speed is a tremendous virtue when people are sick.

How can we do what you are saying so that we can get a better handle on pricing and ensure fairness for the consumer and still do it fast?

Mr. SCHONDELMEYER. At some point, all of the health care industry, including pharmaceuticals, will have to admit they are aware of a process called "cost accounting," and they will have to begin to share that information with us.

I would comment that an NIH researcher who discovered these products through funding from NIH, has a very meticulous cost-accounting process and level of accountability and validation or checking to see how those funds were spent. Yet, the products and information we give away, we don't have any such cost-accounting process.

So, I think it is critical that at some point we begin to get a sufficient dialogue with the industry that they will share their cost-accounting data and quit telling us that it is so much witchcraft and so complex you couldn't possibly do it. This industry is quite capable of solving complex problems and they demonstrate that by bringing valuable new products to the marketplace, and I can't believe they also aren't capable of solving the complex problem of how to price a drug.

They are doing it internally already, so there is enough expertise for the company to do it internally and the financial analysts to do it. Why can't we find a few of those people in the Government or in the private sector who act in the public interest, at least?

I think cost accounting is a necessary part of health care in the future and of pharmaceutical care, also.

Chairman WYDEN. So, you are of the view that it would be possible to get this data with fairly commonly used cost accounting principles? In the instance of drugs like Taxol and Ceredase, which we have spent considerable time on this morning, the public, the taxpayer, through the Government, could have gotten access to that information without extended periods of time, extra expense, and hassle?

Mr. SCHONDELMEYER. Again, if we plan it out a priority, it can be done, just like discovery of that drug can be done even though it was quite complex.

Chairman WYDEN. Dr. Arno, the pharmaceutical companies and you have touched on the question of monopolies and whether or not they are necessary. The pharmaceutical companies say that without the ability to set the price as they see fit, the companies won't participate in CRADA's or work with codeveloped drugs. You seem to take the view that this monopoly argument is not borne out by the cases you have looked at, and that if the monopoly wasn't there, other people would jump in and have at it?

It is a "good dose of free enterprise" argument that you are making, and I wonder if you could flesh out that position a little more.

Dr. ARNO. I think the simplest way to do that is to look at the social and economic rationale we use to grant monopolies in this society. The reasons, I think, are pretty straightforward: To stimulate innovation.

However, if the innovation was made at the taxpayers' expense, by scientists working for the U.S. Government, then it was not made by the pharmaceutical industry. What we are stimulating are excessive profits for the drug company that is handed an exclusive license.

I didn't say that a monopoly should never be granted under any circumstances. But under circumstances such as these, such as the development of Taxol, such as the development of drugs where the Government has done the innovation, we are not stimulating innovation by granting that monopoly. We are merely transferring wealth to the pharmaceutical industry.

Let me just touch on the point that Steve just mentioned vis-a-vis cost accounting and the complexities involved in accounting this. I say that we do much more complex cost accounting already in the health care realm, when we talk about trying to figure out the cost to run a hospital and provide hospital services. There can't be too many things more complex than that.

So, cost accounting has been long delayed in health care in general, for a variety of reasons. But we are doing it with hospitals; we are doing it with physicians, both of which are very complex services, and doing it for pharmaceuticals would be relatively easy in comparison.

Chairman WYDEN. Now, you speak of an independent commission so as to get the NIH and other Government science agencies out of the responsibility of having to make these judgments. Every time at home anybody mentions another agency or another commission, everybody's blood curdles.

Dr. ARNO. Let me clarify. I mentioned it in terms of the appropriate place in the Government to do this cost accounting. I suggested it not be NIH, because for one thing, they don't seem to be terribly interested in doing it.

Chairman WYDEN. That was very clear.

Dr. ARNO. That was made much more clear today than in the past. Second, they don't have the expertise. So, why not give it to the Government bureaucrats who are good at this, like those at the Health Care Financing Administration?

They are setting prices for physician reimbursement. Let them set prices for pharmaceutical reimbursement.

The point about the independent commission was merely to suggest we are moving in a very administrative, regulatory fashion in health care, in those two important segments of the health care environment, hospitals and doctors, and whether it is an independent commission, or a part of Government, I think that is what we are going to have sooner or later.

Chairman WYDEN. Dr. Schondelmeyer, do you like that idea of saying, well, the health policy people aren't in the place to do it, but HCFA can handle the task of crunching the numbers.

Mr. SCHONDELMEYER. Well, if we have to find a model, I would prefer the model of the PROPAC, the Prospective Payment Assessment Commission and the Physician Payment Review Commission. I think those models have been used in health care, and we have two of them up and operating already. They are responsive to Congress rather than an administrative agency that is implementing a program.

I think those might be even more responsive to your interests and needs than a HCFA agency, that would get bogged down on who was getting paid through Medicare or Medicaid and not take care of the cash patient or an insured patient, so, we don't continue to shift to that patient as we have done in other programs.

Chairman WYDEN. Dr. Garber, do you want to share your views on the Arno proposal?

Dr. GARBER. I actually don't have strong feelings about where this body would sit, but I think it is important to emphasize, as we have said earlier today, virtually every witness, except those from the NIH, and others, object, the first panel, that you need the expertise and the appropriate kinds of accounting and economics. But I would also hasten to add, we would continue to need expertise in the basic scientific processes that lead to the development of the drug. In fact, in our experience with the Ceredase case, there were several areas where we required scientific input that was quite substantial.

For example, how big a step was it to be able to develop a process to purify the enzyme? How big a step was it to discover the modification that made it effective?

I think you need that scientific input. But the scientific input is certainly not sufficient by itself. So, that is one reason why an argument could be made to keep the capability within NIH if, in fact, NIH could pursue such a mandate enthusiastically.

Chairman WYDEN. Well, this has been a very helpful panel, and a good one to end a very lengthy afternoon, because your views really cover almost the entire spectrum, from some who have advocated a very strong Government role on pricing, to others who have said the drug company and NIH say it is the way to go, therefore, we ought to just let them go at it.

My sense is, though, that if there isn't a more reasonable way to justify the taxpayer investment in these kinds of areas, there will be considerable support in our country for going to something that involves more Government than I, frankly, feel comfortable with.

I think that the alternative here is to come up with a reasonable justification process or see these prices continue to go through the moon, with more and more people questioning what they are getting for their tax dollars, and support building for Government rate setting and Government sweeping the field.

I saw a comment the other day that what is saddest about this is that if we can't find the balance that we need between incentives to get new products out and incentives for reasonable profits, and a fair pricing process, then one way or another our citizens will pay. They will pay either with their lives, or they will pay with their dollars. That, in my view, is unacceptable.

You all have been very patient. I have found that people who are pursuing this issue are ones that have very strong views and push them eloquently, but are willing to look at other points of view. If we are going to get this resolved, ultimately, it is going to come about because companies, patient advocates, taxpayer groups, academics, and agency people say, look, we are just going to insist on a more reasonable process than we have now, which leaves so much of the citizens' concerns unaddressed, and leaves people understandably fuming about the prospect of having to get divorced to pay for a drug bill, or lose their home, or some of these other tragedies that we have heard about.

So, we thank you.

Ms. Stovall, would you like to add anything?

Ms. STOVALL. At the risk of becoming a potted plant here among these men, I really just wanted to add something that I didn't hear expressed here today, and that is that I know there is an awful lot of good science sitting on the shelves at the Cancer Institute that may never go forward if CRADA's are discouraged or we put too much regulation into the process.

I think that all the things that have been said here today are very thoughtful, but I also think we need to ask NCI to look at the partners that they are, perhaps, maybe sleeping with here in these arrangements, and be very judicious about who they select. I didn't hear that expressed here today.

But I think we have to trust their judgment, in some cases, as to forming good work relationship with the private sector and trust they are going to be able to continue doing that to the best of their ability at some level.

Chairman WYDEN. It is an interesting comment you make. The CRADA process has changed. I have not discussed it this morning with any of the witnesses. Originally there were an awful lot of small companies that were getting CRADA's, and we have consistently found in a lot of areas that these small companies are where you see the inventiveness and the entrepreneurship.

For example, in the case of RU 486, three companies wrote us and said they are willing to show the guts and the fortitude to take on the political far right. They are all small companies. What has happened in the CRADA process is that big firms play a very large roll, whereas smaller firms used to be more significant. Big companies desire to get into this process knowing that as of now, the Government isn't going to insist on much in terms of cost justification and the like.

So, I want you to know that your interest in getting that important work off the shelf, in my view, is as important as any issue in front of the Government, and we are going to pursue it vigorously. The idea is going to be to get it off the shelf as fast as possible and also to make sure that it is fairly priced. We want to work with your organization and with all the groups that have come today.

We do have a new ranking minority member who is going to be a good addition to our subcommittee, Congressman Combest. We are going to hold the record open for him and our colleagues on the majority side to have statements and the like.

Unless you all have anything further to add, we are going to excuse you at this time.

Anything further from any of our witnesses?

The subcommittee is adjourned.

[Whereupon, at 2:05 p.m., the subcommittee was adjourned, subject to the call of the Chair]

APPENDIX

OPENING STATEMENT

REPRESENTATIVE RON WYDEN
BEFORE THE SUBCOMMITTEE ON REGULATION AND BUSINESS OPPORTUNITIES AND ENERGY

PRICING OF DRUGS RESULTING FROM COOPERATIVE RESEARCH AND DEVELOPMENT BETWEEN FEDERAL LABS AND PRIVATE INDUSTRY

January 25, 1993

Today the Subcommittee on Regulation and Business Opportunities continues its inquiry into pricing of drugs developed with significant governmental support. This subject has been a Subcommittee priority because as drug prices continue to skyrocket, a growing percentage of drugs are brought to the marketplace with the taxpayer having funded much of the research through federal lab support and corporate investment tax credits. In fact, up to half of the most valuable cancer and AIDS drugs are developed with substantial taxpayer support.

And through the Orphan Drug Act, government supports the research and development of drugs like Ceredase, which treats a fatal immune disorder. As we shall hear, today, this drug is so expensive that many middle class Americans simply can't afford to buy it.

The Subcommittee and the witnesses appearing today will be discussing a number of these drugs, but the Subcommittee intends to use Taxol, described by the National Cancer Institute as the most promising anti-cancer drug in the last 15 years, as a case study. Residents of the Pacific Northwest are especially interested in this issue because the current, primary source of Taxol is from the bark of the Pacific Yew tree, a species native to the forests of Oregon and Washington.

The public policy questions in front of our Subcommittee are emblematic of the health care crisis facing our country. Americans want new cures for dread diseases on the market as quickly as possible. Americans feel just as strongly that those cures must be affordable. Last year, Americans spent $59 billion on prescription drugs. Much of that therapy came from the seven major U.S. pharmaceutical companies, companies which enjoyed immense profit increases during the last decade.

The federal government, in attempting to respond to concerns that new drugs be made available, quickly at affordable prices, has developed a significant technology transfer program utilizing cooperative research and development agreements (CRADAs) wherein government lab discoveries are made available to private drug companies.

This cooperative process between government and private enterprise should be encouraged because it can bring promising drugs to ailing Americans more quickly than otherwise would be the case. At the same time, drug companies must not be allowed to exploit the taxpayer by charging prices that are unreasonable. The challenge for the federal government is to develop a policy so that our citizens don't have to choose between getting sick or going broke.

In the instance of Taxol, there are a number of facts that are not in dispute:

1. In a September 10, 1991 letter to the Chair, Dr. Samuel Broder, Director of the National Cancer Institute wrote, "Taxol was discovered and developed within the NCI's comprehensive anticancer drug development program."

2. In the same letter, Dr. Broder said that NCI was responsible for "(1) the initial collection and recollection of bark; (2) all biological screening in both cell culture and animal tumor systems; (3) chemical purification, isolation and structure identification; (4) large-scale production, from collection of bark through preparation of material suitable for human use; (5) development and production of a suitable intravenous dosage formulation; (6) preclinical toxicology; (7) filing of an Investigational New Drug Application (INDA) with the FDA, along with all required documentation; and (8) sponsorship of all activities, including efforts directed toward total and partial synthesis of the drug, have been supported through NCI research grants and intramural programs."

   The collective cost of this federal assistance was $32 million dollars at the end of fiscal year 1992.

3. The federal government has said that all "new and raw data from federally-funded research would be "available exclusively to Bristol-Myers Squibb" when the company is "engaged in the commercial development and marketing of Taxol."

4. The Bush Administration gave Bristol-Myers Squibb virtually exclusive access to Pacific Yews on federal forest lands. Beyond a management fee, the company pays virtually nothing for this only approved source of medicinal Taxol.

5. In a December 3, 1992, letter to the Chair inquiring as to whether Bristol-Myers Squibb has provided any pricing analysis for Taxol to the federal government, NIH responded that, "BMS has indicated that it will not provide detailed information about its costs to NIH."

6. Because Bristol-Myers Squibb will divulge nothing about the elements used in establishing the price of taxol, an arbitrary price has been established by determining that Bristol-Myers Squibb may charge a price similar to a range of other arbitrarily priced drugs.

7. The production price paid by the National Cancer Institute for experimental quantities of refined taxol ranged between 60 cents and 90 cents per milligram. Bristol-Myers Squibb has announced it would price the drug at $986 per three-week treatment cycle, or about $4.87 per milligram -- a mark-up of six to eight times the NCI's production cost prior to the agreement.

8. Wall Street analysts say that Taxol will achieve worldwide sales of up to $800 million per year.

9. There is no legal restraint on the right of Bristol-Myers Squibb to patent Taxol analogues or synthetic substitutes.

These facts call into question the foundations of the public-private drug development partnership. As long as Bristol-Myers keeps secret and confidential all matters relating to its development costs, who could know if the price is justified? Given the government's role in developing these drugs, Americans believe that Congress should do more than accept a "trust us" argument from the pharmaceutical giants of America.

In the instance of Taxol, because Bristol-Myers has decided that its federal partner and investor does not need to know how it sets its prices, Congress is left with the question: Were Bristol-Myers' development efforts aimed at discovering, or purchasing, a synthetic -- and patentable -- alternative to bark-produced Taxol to solidify the company's competitive position in the anti-cancer drug market? Again, taxpayers and consumers are in the dark.

Bristol-Myers and other companies claim that if the government insists on answers to these pricing questions they will walk away from the table and that sick Americans will die as a result. They have said, "Do it our way, or no way" betting on the prospect that the desire for new cures is so great that no one will insist on data justifying the taxpayer expenditures.

Those days are over. American consumers who have funded drug development through the gift of corporate tax credits and federal lab research should not be bludgeoned by price gouging. There are limits to what Americans ought to pay for drugs developed through billions of dollars in federal research and federal tax credits. Americans should not be held political hostage to drug companies who threaten to walk away from cures if Congress requires reasonable price justification.

We need rules so that government can assist private companies in getting blockbuster drugs to market quickly, while ensuring our tax dollars are spent wisely -- and that private companies can still make a reasonable profit.

To this end, a number of ideas have been advanced:

- Before entering into a cooperative venture, the drug price would be negotiated based on a formula that estimates the cost and profits of the new drug.

- The NIH could commission an informal panel of experts to assess the price proposed by a company. The panel would work on a confidential basis, but with access to proprietary cost and investment data held by the company.

- On a more formal basis, the NIH, or the Department of Health and Human Services could form a permanent secretariat on pricing, including expertise in the appropriate areas of analysis. The secretariat would give a yea or nay as to whether the minimal thresholds for fair and reasonable pricing specified in the CRADA has been met.

- Paralleling arrangements used for defense contractors, agreements could include stipulations for cost-plus charging, allowing the manufacturer to recover investment and a guaranteed rate of return.

- The Industrial Biotechnology Association suggests that rather than focusing on fair pricing arrangements, a richer profit sharing arrangement for the federal labs should be agreed to by the NIH and its industry partners.

- Dr. Bernadine Healy has suggested that a clear pricing restraint preamble be added to the current CRADA, signifying that the cost of these co-produced drugs is a threshold issue for entry into a cooperative venture.

The Chair is not wedded to any one of these proposals, but I want to note that the drug companies seem to be against every one of them. I believe strongly that this issue is too important to get lost in the Congressional fog. My principle interest is to work quickly now with my colleagues in Congress, the new Secretary of Health and Human Services, drug companies, patient advocates, and taxpayer groups to amend the technology transfer program so that new drugs get to the suffering as quickly as possible -- but ensures fair pricing, as well.

The Subcommittee thanks our witnesses for their cooperation and looks forward to working with all of them in the days ahead.

Testimony of

Dr. Bruce Chabner
Director, Division of Cancer Treatment

Before the

Subcommittee on Regulation,
Business Opportunities, and Energy
Committee on Small Business
United States House of Representatives

Hearing on
The Pricing of Taxol® and Enforcement of
Fair and Reasonable Provisions in
Cooperative Research and Development Agreements (CRADAs)

January 25, 1993

Mr. Chairman and members of the subcommittee, thank you for inviting me to testify before you today regarding the pricing of taxol and enforcement of fair and reasonable provisions contained in Cooperative Research and Development Agreements, or CRADAs, resulting from cooperative ventures between federal laboratories and private manufacturers. I am Dr. Bruce Chabner, Director of the Division of Cancer Treatment, National Cancer Institute (NCI). I am accompanied today by Mr. Reid Adler, Director of the Office of Technology Transfer, National Institutes of Health, and by Dr. Michael Friedman, Associate Director, Cancer Therapy Evaluation Program, NCI.

I welcome the opportunity to testify before you on NCI's experience in collaborating with industry to develop the new anticancer drug, Taxol®. I am also pleased to report that on December 29, the Food and Drug Administration approved Taxol® for use in treating refractory ovarian cancer. With the recent approval of Taxol® and the announcement of a pricing strategy by Bristol-Myers Squibb (BMS), NCI feels that the objectives of the CRADA were satisfied. The overall strategy developed by BMS provides a reasonable approach to the many complex issues related to developing and marketing this important drug. Features of this strategy include: 1) providing Taxol® free to those currently receiving it on a compassionate basis; 2) ensuring access to the drug for indigent patients who cannot afford it or who are uninsured; 3) assisting physicians to work with private and government insurers to obtain coverage for their patients; 4) continuing to provide sufficient quantities to NCI for research purposes free of charge; and 5) establishing a tiered pricing structure with discounts for physicians, Medicaid, Federal Supply Schedule, and the Public Health Service. The pricing scheme announced by BMS for Taxol® compares very favorably with other cancer agents, particularly in view of the significant production costs and its lack of patent protection. In this regard, NCI believes that BMS has been a responsible partner in this CRADA, and this collaboration could serve as a model for cooperation between Government, industry and academia for the benefit of the public. Further, we must remember that market forces, i.e., competitors to Taxol® such as analogues and synthetically produced drug, will influence its price.

Specifically, my testimony will address the issue of the pricing of Government discoveries transferred to the private sector. However, I would first like to explain why collaboration with industry was essential for developing Taxol®.

Taxol® was originally isolated in 1971 from the bark of Taxus brevifolia, although subsequently we have found that it is also present in the bark and needles of a variety of other taxus species. Although Taxol® showed minimal activity in initial preclinical testing, it was later demonstrated to have a unique biochemical mechanism of action and a high degree of activity in selected non-human test systems. At each step, significant problems of production, supply, formulation, and clinical toxicity hampered its development. In 1988 preliminary activity against ovarian cancer was first observed, and in subsequent trials the drug produced response rates of about 30 percent in patients who had failed standard therapy, with some of these responses lasting more than one year.

Taxol® has also demonstrated significant activity against breast cancer and is being tested for activity against several other types of cancer. This is a promising new therapy for many thousands of cancer patients and its development is a very high priority for NCI. Its purification to a form that can be administered to patients presented a very formidable obstacle, and only gram quantities, enough to test in a few hundred patients per year, were produced by NCI in the early years of its experimental development. The first promising signs of antitumor activity were reported in 1989, but further development and marketing required an industrial partner. NCI could not offer market exclusivity, because the drug had not been patented by NIH and had entered the public domain and was therefore unpatentable. However, the Federal Technology Transfer Act (FTTA) of 1986 did allow the negotiation of a CRADA.

Since the passage of the Stevenson-Wydler Technology Innovation Act of 1980 and the FTTA of 1986, it is a national policy to transfer federally-owned or originated technology to the private sector whenever appropriate. The Act also encouraged, as a national policy, joint research and development projects between government laboratories and industry. Indeed, these are duties of each laboratory. NCI has followed the policy of seeking partners in private industry to commercialize its discoveries and inventions. In order to assure the further development of Taxol® and eventual marketing of the drug, in 1991 NCI entered into a CRADA with BMS. The purpose of this CRADA was to expedite the development of Taxol® as an antitumor agent, to generate data necessary to obtain FDA approval of the compound, and to develop alternative sources of the drug as soon as possible.

The CRADA was awarded to BMS following a full and open competition, including publication of a solicitation in the Federal Register, and a thorough scientific review by government scientists of four separate proposals submitted by (1) Bristol-Myers Squibb, a major international pharmaceutical company in the field of cancer drugs; (2) Rhone-Poulenc, a major French firm that had no track record in the cancer field, but currently is developing a close analogue of the drug Taxol® called Taxotere, which we expect will be a major competitor of Taxol®; (3) Lyphomed, a small American subsidiary of a major Japanese firm (Fujisawa); and (4) Unimed, a small American company with no experience in the cancer field. BMS was chosen after careful deliberations by an expert panel of NCI scientists knowledgeable about the drug development and testing process, and in January of 1991 agreed to terms with NCI.

In seeking our CRADA partner, we asked that, in exchange for exclusive access to our data for purposes of obtaining FDA approval, our partner would be obliged to produce the drug in amounts required for research and development; cooperate with us in executing a broad research agenda; assure access for all patients needing the drug; and set a fair market price. However, there was no specific guidance on how a fair and reasonable price would be viewed by NCI. Taxol® represents the second instance in which a therapy subject to a fair price clause has been approved for marketing. The first was NCI's licensing of the AIDS drug, ddI, also to BMS. In that instance, the price of ddI, or Videx® announced in the spring of 1991, was far below that of the entry price of its competitor, AZT, and the company was praised publicly for its forbearance.

In recognition of the need to establish a fair and reasonable price for Taxol®, the text of the CRADA also includes an acknowledgement by BMS that in developing a fair market price for Taxol®, consideration will be given to the public investment in Taxol® research and development and the health and safety needs of the public. Because Taxol® is not patented, other companies are able to develop Taxol® analogues, some of which conceivably might be more effective and less toxic than Taxol® itself. We believe that these market forces also will limit the price of Taxol®.

During the past year, NCI grantees have made significant progress in developing alternative sources of Taxol®, including total synthetic production; alternative renewable resources, such as needles and twigs as sources of Taxol® or Taxol® precursors, which can be converted to Taxol® by partial synthesis; cultivation of faster-growing taxus species, plant tissue culture, hydroponics; etc., all of which would eventually eliminate the need for tree bark. The NCI is also encouraging other private pharmaceutical companies to enter the search for active Taxol®-like compounds that do not require extraction from tree bark. In fact, NCI entered into a CRADA with Rhone-Poulenc, a BMS competitor, to aid in the testing of a Taxol® analogue, Taxotere. Taxotere appears to have promising clinical activity in ovarian cancer, and the company holds several patents on this compound. NCI has joined the company in testing taxotere as a single agent and in combination with other therapies against ovarian cancer, lung cancer and other common solid tumors. As Taxotere is manufactured from precursors found in yew needles, the company is not dependent on the harvest of trees for its production.

Since 1991, BMS has exceeded its contractual obligations. With the aid of the U.S. Department of Agriculture, the Department of Interior, and the Congress, BMS has been given access to yew bark from trees on Federal lands, and now produces Taxol® in commercial amounts. Alternative semi-synthetic sources have been identified, that will free BMS from dependence on the Pacific yew. Clinical trials supported by the CRADA partners have yielded evidence of consistent activity in ovarian cancer, and promising early results in other tumors. On December 29, 1992, BMS received FDA approval of Taxol®. This occurred well ahead of the timetable set by the CRADA.

Implementation of the fair-pricing clause has required the NCI to consider several options. We considered the possibility of conducting a detailed cost analysis of the proposed price, but rejected this alternative because a cost-based analysis is significantly complicated by NCI's lack of expertise in pharmaceutical price setting. NCI believes that such a policy will discourage future collaborations between government and industry, which in effect, will undermine the intent of the FTTA, namely to encourage the transfer of technology to the private sector. A number of intangible and unqualifiable factors contribute to a "fair" price, including the market life of the product, the period of market exclusivity, potential competition of related products, and anticipated market size, all of which defy precise delineation. Furthermore, the CRADA did not require the company to disclose proprietary information regarding total costs of production development and marketing, and the company exercised its right not to disclose such information.

In the absence of a detailed price analysis, the value of the pricing clause has been called into question. There is little difference between the terms "fair" and "reasonable". In the context of our CRADA with Bristol-Myers Squibb, the intent of the clause was to seek a price that takes into account the major government investment, and the health needs of the public. Also taken into account were those factors that pharmaceutical companies normally consider in setting prices, which could include market prices for comparable drugs and production problems.

The CRADA mechanism through which the pricing clause has been included is an extremely useful vehicle. It has made the pricing issue a matter of public interest; in so doing, this clause has undoubtedly exerted considerable pressure on the company in question to moderate its pricing strategy. Specifically, it has allowed the NCI to argue forcefully for total access to the drug, both for those that can afford it and those unable to pay. It has allowed us to guarantee that the thousands of patients already receiving Taxol® on a compassionate basis will continue to receive the drug free, even though Taxol® has been approved by the FDA.

As previously mentioned, NIH lacks the expertise to undertake a cost-based analysis. Therefore, we chose instead to measure the fairness and reasonableness of Taxol®'s price by comparison with other products marketed for the same indication. We requested that the company set the price of Taxol® below the median for other recently approved anticancer drugs. We felt that these conditions were fair, since, in our experience, Taxol® was exceedingly expensive to produce. From 1983 to 1991 (prior to the CRADA) NCI produced

Taxol® for its own clinical trials and other research use, as we had similarly produced Cisplatin for our own use. Taxol® was at least 10-fold more expensive to produce than Cisplatin, the drug now considered the primary agent for treating ovarian cancer.

Beginning in the summer of 1992, NCI staff met on three occasions with representatives from BMS to discuss their pricing strategy, and emphasized the need to assure that all patients requiring the drug would have access to it. We believe BMS's pricing strategy announced on December 29, 1992, is consistent with that goal for the following reasons: 1) the wholesale price would lead to a cost per cycle of ($980) for the average patient, which is less than the cost of carboplatin ($1,030) and less than other recently approved anticancer drugs, such as deoxycoformycin, idarubicin, BCG, mitoxantrone, ifosfamide, G-CSF, and GM-CSF. Only zoladex, flutamide and levamisol, all relatively simple molecules to produce, cost significantly less than Taxol®; 2) those unable to afford the drug will receive it free through the company's indigent program; 3) medical and government institutions will receive the drug at a significant discount; 4) thousands of patients currently receiving Taxol® under a broad compassionate-release program will continue to receive it free after FDA approval; 5) the drug will be provided free for research trials sponsored by NCI; 6) the price will be adjusted as indications for Taxol®'s use broaden and the market expands; and 7) the price in the United States will be lower than that in Canada.

The net-weighted cost of Taxol® for American patients will be equal to the wholesale price of cisplatin, despite the fact that cisplatin is inexpensive to produce, has a much larger market than Taxol®, and has been covered by patent protection for the first 15 years of its commercial sale. Thus, NCI believes that the pricing strategy announced by Bristol meets any reasonable test of fairness, if one considers the price of similar products, its lack of patent protection, and the significant problems in its production. In this instance, the FTTA allowed a very effective transfer of technology to the private sector, with all the advantages of rapid scale-up of production and rapid commercialization, and with assured access of all women with ovarian cancer who require this treatment. The success of this collaboration should offer strong encouragement to companies contemplating similar ventures with Government laboratories, and this collaboration can only bring better health and a stronger economy to the American public.

You asked for our opinion as to the utility of a fair pricing clause in CRADAs. NCI believes that it should be retained; it appears to place a spotlight on price and puts the company on notice that its pricing policy will receive public scrutiny. A second, and equally important provision is the statement of the principle of providing access for all patients that need the drug. This provision in effect leverages NCI's efforts to have the company establish an indigent program and to continue providing drug under compassionate release mechanisms. In the case of Taxol®, I believe our negotiations regarding a fair price produced the desired results.

The question has been raised as to whether more restrictive pricing language or its enforcement would discourage cooperation between NIH and the private sector. NCI believes that it would. In our recent experience, one company has refused to accept a fair pricing clause as part of a license agreement for an anti-AIDS drug and another has done the same for an anti-cancer drug CRADA. A third company has discontinued its collaboration with NCI on the development of a novel anti-AIDS drug because of fears that the government would use its involvement as a reason to impose price restrictions. A fourth company has suspended negotiations for cooperative development of two cancer drugs pending the outcome of the Taxol® pricing hearings. Other companies have simply refused to become involved with the NCI in early drug development, and although the reasons were not stated openly, fears about price control play a significant role. NCI has no doubt that companies will not accept the risks of investing large sums in the development of a government product if their freedom to realize a profit could be restricted. These companies are not willing to put their corporate fate in the hands of a government-appointed committee of experts. There are less risky way for companies to make a profit.

On December 2, 1992 the Advisory Committee to the Director NIH discussed the issue of drug pricing in detail, following presentations by several distinguished representatives from academia, industry and government. We expect that this issue will continue to be a topic of intense scrutiny within NIH as we work with the new administration in this policy area.

As public officials, we recognize our responsibilities to the American people and to the Congress to ensure that our actions are in the best interest of the public health. We welcome the opportunity to appear before you to address your concerns. I would be happy to answer any questions you may have.

STATEMENT OF
ZOLA HOROVITZ, Ph.D
VICE PRESIDENT, BUSINESS DEVELOPMENT AND PLANNING
BRISTOL-MYERS SQUIBB PHARMACEUTICAL GROUP
BEFORE THE
COMMITTEE ON SMALL BUSINESS
UNITED STATES HOUSE OF REPRESENTATIVES
JANUARY 25, 1993

Mr. Chairman, my name is Zola Horovitz. I am Vice President for Business Development and Planning of the Bristol-Myers Squibb Pharmaceutical Group. I am pleased to have this opportunity to share with you some important information about Taxol® (paclitaxel), a new anticancer agent developed under a Cooperative Research and Development Agreement (CRADA) between Bristol-Myers Squibb Company and the National Cancer Institute (NCI).1/

BACKGROUND

As you know, this is my second appearance before the Subcommittee. I first testified on July 29, 1991, barely six months after the Taxol® CRADA was signed. At that time, I explained the competitive process through which Bristol-Myers Squibb had been selected by the NCI to be its private-sector

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1/ A background paper on Taxol® and the CRADA process is attached at Tab A.

collaborator in the Taxol® development project, and noted a number of difficult problems, principally related to drug supply, that previously had hindered Taxol® development.[2/]

Immediately after the CRADA was signed in late January of 1991, Bristol-Myers Squibb designated Taxol® as its top research priority and set four aggressive goals in an effort to make Taxol® available to cancer patients at the earliest possible time. I never doubted the Company's commitment to the project, or the strength of its expertise in the development of anticancer drugs. However, based on the limited data available at that time, and the magnitude of the known challenges, I was concerned that these goals were too ambitious to be realistic. Today, however, I am able to state unequivocally that Bristol-Myers Squibb has actually exceeded all four of its ambitious performance goals, and has done so substantially ahead of schedule.[3/]

CRADA GOALS

1. Increase Supplies of Pacific Yew Bark

Our first objective for 1991 was to gather 750,000 pounds of Pacific yew bark, the raw material that currently is the only approved source of Taxol® for human use. This target was dramatically higher than actual collection levels in previous years; however, with the active assistance of Hauser Chemical

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[2/] A chronology of the Taxol® development project is attached at Tab B.

[3/] A chart summarizing Bristol-Myers Squibb's CRADA achievements is attached at Tab C.

Research, the Forest Service and the Bureau of Land Management, we actually collected roughly 825,000 pounds of bark from federal lands in 1991, and a comparable amount in 1992. An equal amount of bark was collected from private lands as well.

2. **Increase Supplies of Taxol®**

The success of the bark collection program allowed us to meet and exceed our second objective, which was to provide NCI with one kilogram of formulated Taxol® in 1991 for use in clinical trials. In prior years, NCI had obtained an average of one-half kilogram of Taxol® per year. Bristol-Myers Squibb more than doubled that amount in 1991, exceeding our own objective by more than one-third.

In January of 1992, we increased shipments fivefold -- from 5,000 to 25,000 vials per month -- and, from April through December, we made 50,000 vials of Taxol® available to the NCI each month. In sum, the quantity of formulated Taxol® available to the NCI in 1992 was more than 30 times greater than the amount available in 1990, the year before the CRADA was signed. These dramatic increases in monthly shipments of formulated Taxol® -- all of which were provided free of charge -- enabled the NCI to accelerate clinical trials and to initiate compassionate use protocols through which more than 4,800 cancer patients had been treated with Taxol® by the end of 1992.

3. **Develop Alternative Sources of Taxol®**

During the same period, Bristol-Myers Squibb initiated an aggressive search for alternative sources of Taxol® so that reliance on Pacific yew bark collected from the wild could be eliminated within five to eight years. Ordinarily, in a project of this type, we would have identified a range of possible alternatives, set priorities, and explored the most promising approaches first. In the case of Taxol®, however, we chose to pursue several alternatives simultaneously.

Since early 1991, Bristol-Myers Squibb has committed millions of dollars to this comprehensive effort, which involves research in its own laboratories and more than a dozen collaborations with various companies, researchers and academic institutions. The Company and its collaborators are engaged in a variety of research and development projects, including yew cultivation on a commercial scale, the manufacture of Taxol® from a chemical precursor produced from renewable biomass, the production of Taxol® in a plant cell culture, and total synthesis of the Taxol® molecule.[4/]

This comprehensive approach increased the complexity and cost of the effort, but it also produced meaningful results much more quickly than expected. In fact, I am pleased to be able to report that significant amounts of Taxol® will be produced by semi-synthetic means in 1993, and that we expect to eliminate the need for Pacific yew bark by the end of 1995 -- several years ahead of schedule.

[4/] Additional information about the search for alternative sources of Taxol® is provided at Tab D.

4. File an NDA within Four Years

The fourth objective -- clearly the most important -- was to file a new drug application (NDA) within four years of signing the CRADA. Bristol-Myers Squibb actually filed an NDA on July 22, 1992, only 18 months after the CRADA was signed.

TAXOL® APPROVAL

Although Bristol-Myers Squibb's performance with respect to these four CRADA goals is indicative of substantial achievement, there is one far more important measure of the true success of the Taxol® project to date -- the Food and Drug Administration's (FDA's) expeditious review and approval of the NDA. Within four months of the date on which the NDA was filed, FDA had completed its evaluation of the data package, and had submitted the application to its Oncologic Drugs Advisory Committee for review. Five weeks later, on December 29, 1992, just 23 months after the CRADA was signed, Bristol-Myers Squibb received FDA clearance to market Taxol® for use in the treatment of refractory ovarian cancer. Today, Taxol® is widely available to patients through oncologists and hospitals nationwide.

But the approval of Taxol® for an initial indication does not indicate that the project is complete. In fact, ongoing work with respect to the development of alternative sources will proceed on schedule, and Bristol-Myers Squibb will continue to supply free drug to the NCI, so that a variety of additional potential uses of Taxol® can be evaluated. Clinical trials designed to evaluate the safety and efficacy of Taxol® in the treatment of breast cancer, non-small cell lung cancer, and several other tumor types are already underway. The use of Taxol® in combination with other anticancer agents will be explored as well. Thus, the CRADA will remain in effect as the NCI and Bristol-Myers Squibb work together to develop Taxol® to its fullest potential.

Even though the project is not yet complete, FDA's approval of Taxol® must be viewed as a milestone in at least three respects. First and foremost, it ensured that a very important, novel anticancer agent -- one that the NCI has called the most important to be developed in the last decade -- was made available to cancer patients at the earliest possible time. Second, the FDA review period for Taxol® was one of the shortest ever, and almost certainly the shortest for an anticancer agent -- a record that reinforces the value of the FDA policy promoting expedited review of drugs for life-threatening diseases. Finally, because Taxol® is the first significant drug to be developed under a CRADA, its approval provides tangible evidence that the CRADA process, as currently implemented, works as the Congress intended -- that collaborative research and development projects can yield meaningful results of measurable practical value to the American public. For all of these reasons, the Taxol® project should be viewed as a model for future collaborations between government agencies and private companies.

PRICING

The Taxol® project also provides a valuable model with respect to the fair and responsible pricing of products developed under CRADAs. In fact, it should become the standard against which the pricing of other products developed under CRADAs will be judged, not only because the process struck a fair balance between the interests and concerns of both CRADA partners, but also because it worked exceptionally well.

1. The Federal Technology Transfer Act

Analysis of the Taxol® pricing process must begin with the governing statute. The Federal Technology Transfer Act of 1986, which authorizes and governs CRADAs, and which was passed with broad bi-partisan support, was designed to provide an efficient mechanism for promoting technology transfer -- for encouraging the conversion of government-sponsored discoveries (such as Taxol®) into products of practical value to the public.

In enacting this legislation, Congress recognized the need to provide strong financial incentives to stimulate private sector participation in collaborative research projects. Consequently, the Technology Transfer Act expressly permits federal laboratories (such as the NCI) to negotiate directly with private sector collaborators, and authorizes the granting of exclusive commercialization licenses to private companies on reasonable terms. However, Congress did not authorize government agencies to set or regulate the price of products developed under CRADAs.

2. NIH Policy

Nonetheless, beginning in late 1987, the National Institutes of Health (NIH) began asking collaborating parties to agree to a "reasonable pricing clause" in connection with the exclusive licensing of government-owned inventions protected by patent. Since that time, this policy has been applied routinely in the context of CRADAs involving exclusive patent licenses, although the NIH is the only federal agency to impose such a requirement on its CRADA partners.

3. The Standard NIH Pricing Clause

Because the "reasonable pricing clause" has no statutory basis, and because a number of potential collaborators have been reluctant to agree to pricing restrictions of any kind, the precise language of the clause has varied from time to time. Typically, however, the standard "reasonable pricing clause" includes two elements: (1) a declaration of the government's "concern that there be a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public;" and (2) a statement to the effect that the government "may require that this relationship be supported by reasonable evidence."

4. The Videx® Pricing Clause

Bristol-Myers Squibb agreed to include an early version of this standard clause in the exclusive commercialization license to Videx® (ddI), a patented AIDS drug discovered by the NCI, and subsequently developed by Bristol-Myers Squibb. In fact, Videx® is the only product that has come to market under an agreement containing the standard NIH pricing clause. When Videx® was introduced in October of 1991, Bristol-Myers Squibb established a price considerably lower than that of the only other comparable product then on the market. The Videx® price was almost universally viewed as reasonable, and Bristol-Myers Squibb was publicly commended for the manner in which it honored its reasonable pricing obligations.

5. The Taxol® Pricing Clause

At the time the Taxol® CRADA was awarded, the standard "reasonable pricing clause" was being included routinely in NIH exclusive commercialization licenses. Initially, the NCI requested that it be included in the Taxol® CRADA as well. However, because Taxol® is not patentable and therefore could not be the subject of an exclusive patent license, the parties agreed that use of the standard clause would not be appropriate. Instead, the NCI and Bristol-Myers Squibb agreed to negotiate pricing language tailored to the specific facts and circumstances of the Taxol® project.

For that reason, the pricing language of the Taxol® CRADA is unique. It does not focus solely on the NCI's concern that there be a reasonable relationship between the pricing of Taxol®, the public investment in Taxol® research and development, and the health and safety needs of the public. Rather, the CRADA contains reciprocal acknowledgements of the parties respective concerns about pricing, and requires that all of these concerns be taken into account in establishing a fair market price for Taxol®. Thus, Bristol-Myers Squibb's concerns about the lack of patent protection, and about the complexity and expense of the Taxol® development project, are included among the factors to be considered in connection with Taxol® pricing. In addition, the Taxol® CRADA imposes no requirements with respect to the submission of evidence to explain or justify the Taxol® price.

6. The Taxol® Pricing Process

Neither the standard pricing clause nor the pricing language of the Taxol® CRADA establishes a formal process for evaluating the prices of products developed under CRADAs. However, building on experience gained in the pricing of Videx®, Bristol-Myers Squibb and the NCI consulted informally with respect to Taxol® pricing issues on several occasions in the weeks preceding NDA approval. These informal discussions provided an opportunity for the parties to exchange information about the project and to share their respective concerns about pricing issues.

As a result of these discussions, Bristol-Myers Squibb prepared and submitted to the NCI a lengthy document describing key factors considered in setting the Taxol® price.5/ That document demonstrates that Bristol-Myers Squibb honored its CRADA obligations with respect to the consideration of a wide range of factors relevant to the pricing of Taxol®, including the NCI's investment in Taxol® research and development.

5/ A copy of the document is attached at Tab E.

In addition, at the time Taxol® was approved, Bristol-Myers Squibb provided the NCI with a second document describing the details of the Taxol® pricing structure,[6] including rebates and discounts provided to various government agencies and Bristol-Myers Squibb's own patient access and reimbursement assistance programs.[7] On the basis of information contained in that document, NCI concluded that the projected cost per cycle of Taxol® therapy is well below that of many other recently-approved anticancer agents and is in the mid-range of other agents currently used in the treatment of refractory ovarian cancer, and that Bristol-Myers Squibb had taken appropriate steps to assure that no patient would be denied the drug because of inability to pay -- facts that both Bristol-Myers Squibb and the NCI view as strong evidence that the price of Taxol® is fair and responsible.

In sum, Bristol-Myers Squibb and the NCI have created an administrative record sufficient to establish that Bristol-Myers Squibb honored each and every one of its contractual obligations with respect to the fair and responsible pricing of Taxol®.

ISSUES RELATING TO STRICTER PRICE REGULATION

The Taxol® pricing process provides clear evidence that there is no need for stricter regulation of prices of products developed under CRADAs. In fact, more restrictive pricing policies would pose a serious threat to the viability of the NIH technology transfer program.

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[6] A copy of that document is attached at Tab F.

[7] A description of Bristol-Myers Squibb's patient access and reimbursement assistance programs is attached at Tab G.

1. **Lack of Statutory Authority**

As an initial matter, federal agencies lack statutory authority to set or regulate the prices of products developed under CRADAs, or to require CRADA partners to submit detailed information concerning such things as production costs, profits margins, and marketing expenses. Historically, licensees of government-owned products have had broad discretion with respect to pricing licensed products and there is no evidence that the Congress intended to change that practice in any way.

Furthermore, even if NIH had legal authority to regulate prices, the agency could not effectively do so as a practical matter. Drug pricing is a complex task -- one that requires the detailed and ongoing analysis of a wide range of factors, including direct and indirect research costs, raw material production costs, size and characteristics of potential markets, existing and anticipated competition, the nature and extent of patent rights, lost opportunity costs, the policies of third-party payers, and the costs of indigent patient programs.

As Dr. Healy has said publicly, NIH officials are not qualified by training or experience to set pharmaceutical prices. Nor do they have the time, resources or expertise to gather and analyze pricing data, or to engage in detailed pricing reviews. To date, the NIH has signed more than 100 CRADAs. In addition to diverting resources away from key research priorities within the agency, the burden of conducting detailed pricing reviews for all the products in the NIH portfolio could be overwhelming.

2. **Creation of Disincentives**

But perhaps more importantly, the imposition of greater restrictions on product pricing would create material disincentives for private sector participation in the CRADA process. As previously noted, the Federal Technology Transfer Act was intended to encourage technological innovation, enhance international competitiveness, augment federal research efforts, and increase the level of public benefit from government-sponsored research. Properly managed, the CRADA process can promote all of these worthy goals. None of Congress's objectives will be achieved, however, if the CRADA process is politicized or managed in such a way as to discourage full participation by industry.

The federal technology transfer program simply cannot survive without active, enthusiastic industry support. For example, as the premier biomedical research organization in the world, the NIH is a major source of new biomedical discoveries. However, because its mission is limited to the conduct and support of laboratory and clinical research, NIH must depend on private companies to bring those discoveries to practical application -- to bridge the gap between the laboratory and the clinic, and to secure regulatory approvals for new products. Without the assistance of private pharmaceutical companies, many important government-sponsored discoveries would be destined to remain on laboratory shelves, where they would offer little, if anything, of practical value to the patients who could benefit from them, or to the taxpayers who supported the basic research.

Pharmaceutical companies exist in the practical world of commercial reality, where substantial financial incentives are essential to justify the enormous investments and substantial risks involved in building and maintaining the scientific expertise and comprehensive infrastructure required for the rapid development of new products. In the case of Taxol®, for example, in only two years Bristol-Myers Squibb has invested substantially more than the $114 million and 125 staff years set forth in the CRADA, and its investment is several times higher than the NCI's $32 million investment in Taxol® research. Few, if any, companies are willing or able to make investments of that magnitude without some assurance that they will have a meaningful opportunity to recover their investments and earn a reasonable return.

In addition, most potential collaborators are fully occupied in developing their own proprietary compounds. Given finite resources, companies must often defer other important projects of their own in order to become involved in CRADAs. Most companies would prefer to invest in the development of a proprietary compound that can be priced freely, as opposed to becoming involved in a CRADA that unduly restricts pricing discretion.

As a practical matter, any attempt by the NIH to regulate prices, or to second-guess or micro-manage collaborators' pricing decisions, will undermine, and perhaps destroy, the financial incentives necessary to attract private companies to collaborative research projects. According to NIH officials, several companies have declined to become involved in important collaborative research projects because of concerns about the impact of the "reasonable pricing clause" currently in use. Other companies can be expected to withdraw from the process as well, if the NIH attempts to impose additional onerous and unnecessary restrictions on collaborators' pricing discretion.

3. **Pricing Review By An Independent Panel of Experts**

Congressman Wyden has suggested that the NCI assemble a panel of objective drug pricing experts, who would work in confidence to review drug development cost data, assess the initial price of Taxol®, and prepare a report for NCI officials. In previous communications, Bristol-Myers Squibb has expressed strong reservations about the fairness and feasibility of such a plan.

In the case of Taxol®, explicit contractual obligations with respect to pricing were negotiated two years ago, at the time the NCI and Bristol-Myers Squibb were negotiating the final terms of the Taxol® CRADA. Those obligations, expressed in terms of a range of factors to be considered when the Taxol® price was set, were based upon the specific facts and circumstances, and potential risks and benefits, known to the parties at that time. Bristol-Myers Squibb undertook the Taxol® development project in good faith on the basis of these contractual agreements, and honored them fully at the time the Taxol® price was established. To impose entirely new requirements at this juncture would be entirely unjustified and manifestly unfair.

Furthermore, even with respect to future CRADAs, and assuming that there are bona fide "experts" in this field (which, based on my 40 years of experience, I seriously doubt), we question whether the government could assemble a panel of truly "objective experts," or whether such a panel could be expected to adopt or follow procedures adequate to guarantee confidential treatment of proprietary information submitted by private companies. In any event, most companies, including my own, would view the convening of such a panel as a compelling reason not to participate in the CRADA process in the future.

4. **Enforcement of Reasonable Pricing Clauses**

I do not intend to suggest, however, that the NIH has no legitimate role to play in evaluating the performance of collaborators with respect to the responsible pricing or products developed under CRADAs. In fact, there are at least three ways in which the NIH can properly constrain a collaborator's discretion to set prices, without imposing unduly burdensome regulatory requirements.

First, the NIH has broad authority to select qualified and reputable CRADA partners, and to decline to enter into agreements with companies that do not meet high standards with respect to established performance criteria. If the NIH has serious concerns as to whether a particular potential collaborator will act responsibly in the pricing of products developed under a CRADA, the agency can freely choose not to become involved in a research collaboration with that company.

Second, the NIH has an obligation to monitor and evaluate a collaborator's performance to insure that the company is acting responsibly in carrying out all of its statutory and contractual obligations, including those involved in the pricing of products developed under the CRADA. The competitive selection process should give rise to a presumption that the CRADA partner will act responsibly; however, in cases in which there is clear evidence of irresponsible behavior, the NIH can and should ask the collaborator to explain its actions. If the collaborator is unable or unwilling to do so, the NIH can seek to terminate the CRADA on breach of contract grounds.

Finally, the NIH can and should encourage competition in the marketplace, so that market forces will act as a restraining influence on the prices of products developed under CRADAs. In fact, the NCI has actually done just that by working simultaneously with competing companies in the development of two AIDS therapeutics (ddI and ddC) and two anticancer agents (Taxol® and Taxotere®). Fostering healthy competition in the marketplace is perhaps the most effective way to insure that collaborators will establish reasonable prices for products developed under CRADAs.

CONCLUSION

In sum, the Taxol® project provides clear evidence that current NIH policies and procedures are entirely adequate to protect the public interest in promoting reasonable pricing of products developed under CRADAs, without impairing, or perhaps destroying, meaningful financial incentives necessary to encourage enthusiastic participation in collaborative research projects by private pharmaceutical companies. Based upon experience to date, active regulation of prices is neither necessary nor appropriate, and more importantly, was not the intent of Congress.

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BACKGROUND: TAXOL® AND THE CRADA PROCESS

When Congress passed the Federal Technology Transfer Act of 1986, it made research from government laboratories more widely available to the taxpayers who support it. It also recognized that a majority of successful technology transfers rely on the resources and active support of private industry.

The Act is intended to encourage technological innovation, to enhance the international competitiveness of American industry, to augment federal research efforts, and to increase the level of public benefit derived from government-sponsored research.

Government agencies have neither the mandate nor the resources to bring products to market. For example, the National Institutes of Health (NIH) is a major source of biomedical discoveries in the world, but it must rely on private companies to bring its discoveries to practical application -- bridging the gap between the laboratory and medical practice -- and to secure regulatory approvals for new products. Such a collaboration can be formed through a Cooperative Research and Development Agreement (CRADA).

345 Park Avenue New York, NY 10154 0037 Pharmaceuticals Consumer Products Nutritional Products Medical Devices

Federal agencies operate more than 700 laboratories, and hundreds of CRADAs have been established, including approximately 100 with the NIH. Without the involvement of private pharmaceutical companies, many important government-sponsored discoveries would remain on laboratory shelves, where they would offer little, if anything, of practical value to the patients who could benefit from them, or to the taxpayers who supported the basic research.

The CRADA Process

Properly managed, the CRADA process can promote all of the goals of the Federal Technology Transfer Act by functioning as a catalyst for accelerating the conversion of government-sponsored discoveries into products of practical value to the public. Under a CRADA, laboratories of federal agencies can enter into research and development agreements with companies, private or public foundations, and not-for-profit organizations.

In these cooperative agreements, the government may provide personnel, services and property -- everything but funds -- while the private sector partner may provide funds, as well as services, personnel and property. The agreements are structured to move knowledge and technology from government research into the development of new products and processes with the assistance of a commercial partner.

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Although a CRADA partner may be sought by either the federal agency or the private-sector participant, partnerships usually are formed after several companies compete in response to invitations from the agency. After a partner is selected, a contract is created detailing what each party will contribute and receive in the course of the project.

Taxol

The anticancer compound Taxol(R) (paclitaxel) is the first significant drug cleared for marketing as a result of the CRADA process. Its approval and subsequent availability to patients who may benefit from it serves as an example of the effectiveness and value of the CRADA concept.

The potential therapeutic uses of Taxol, extracted from the bark of the Pacific yew tree, have been recognized since the late 1960s. Taxol is an extremely difficult drug to manufacture, and its development had been hindered for a number of years by very limited drug supply. The NCI could only manufacture enough Taxol to treat several hundred patients per year. When clinical trials showed promising results in 1989, the National Cancer Institute (NCI) sought a pharmaceutical partner to collaborate in developing the drug.

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The NCI advertised for applications in the Federal Register, inviting pharmaceutical companies to compete for the rights to be its commercial development partner for Taxol. Approximately 20 companies requested information on Taxol in response to the Federal Register notice. Of these, only four companies submitted proposals.

NCI selected Bristol-Myers Squibb because of its considerable resources and infrastructure, expertise, broad experience with natural products, longstanding success in cancer drug development, and the aggressive plan it submitted to expedite development and make Taxol rapidly and widely available to cancer patients.

The Taxol CRADA

Under terms of the CRADA signed in January 1991, the NCI provides Bristol-Myers Squibb with exclusive rights to clinical and pre-clinical data needed to prepare and submit a New Drug Application (NDA) seeking U.S. Food and Drug Administration marketing approval of Taxol.

Taxol was never patented and no patent is even possible. The only exclusivity or protection afforded the company is the five years of protection from generic competition (Abbreviated New Drug Applications) granted under Hatch-Waxman to every new chemical entity. This limited exclusivity provides no protection against the

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introduction of chemically similar new compounds.

Thus, as a practical matter, the company expects to see competition in as little as two years from another anticancer compound in the taxane family known as Taxotere. Taxotere, like Taxol, is being developed under an NCI CRADA by a French company, Rhone-Poulenc Rorer.

Bristol-Myers Squibb also voluntarily relinquished the seven years of exclusivity that accompanies orphan drug status for Taxol -- even though it qualifies for that designation -- because the company believes that the potential uses of Taxol would place it outside the spirit and intent of the Orphan Drug Act.

Under terms of the CRADA, Bristol-Myers Squibb agreed to take on a number of responsibilities. These include: supplying Taxol to NCI for clinical trials, initiating an aggressive search for alternative sources of Taxol to lessen or eliminate dependence on the Pacific yew, and -- most importantly -- developing and filing the New Drug Application.

Four ambitious objectives were set out for Bristol-Myers Squibb in the CRADA -- all of which have been met or exceeded.

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1. The company agreed to gather, in 1991, 750,000 pounds of Pacific yew bark, which is still the only approved source of Taxol for human use. This target was dramatically higher than collection levels in prior years. Bristol-Myers Squibb actually collected 825,000 pounds of bark in 1991, and an equal amount was collected in 1992. About half of all bark collected was from federal lands.

2. The second objective was to provide Taxol free of charge for NCI clinical research -- specifically, to provide one kilogram of formulated Taxol before the end of 1991, more than twice the amount of Taxol produced in 1990. This ambitious target was exceeded by more than a third with the delivery of 1.35 kilograms of bulk drug (45,000 vials).

In January 1992, Bristol-Myers Squibb increased deliveries to NCI from 5,000 to 25,000 vials per month. In April, the company doubled shipments to 50,000 vials per month. This rate of shipping amounts to an annualized total of 16 kilograms of formulated Taxol -- more than 30 times the Taxol obtained by NCI in 1990, the year before the CRADA was signed.

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3. The company also agreed to initiate an aggressive search for alternative sources of Taxol. Bristol-Myers Squibb originally projected that it would be able to end - reliance on Pacific yew bark within five to eight years. In actuality, much faster progress has been made. The company now reports that significant amounts of Taxol will be produced by semisynthetic means in 1993, and that it expects to eliminate the need for Pacific yew bark completely by the end of 1995 -- essentially accomplishing its objective in half the time originally anticipated.

4. The final objective -- the most important from a patient's perspective -- was to file a New Drug Application within four years of signing the CRADA. The NDA was actually filed on July 22nd, only 18 months after signing the CRADA. The FDA Oncologic Drugs Advisory Committee recommended on November 16 that Taxol be approved, and FDA cleared Taxol for marketing in December, 1992.

Since the CRADA was signed in January, 1991, Bristol-Myers Squibb has made Taxol its number one research priority. In only two years, Bristol-Myers Squibb has invested several times the $32 million spent on Taxol by the government -- and far in excess of the $114 million required by the CRADA. In addition, Bristol-Myers Squibb people have devoted more than 205 staff years to bringing Taxol to the patient

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-- which is far in excess of the CRADA requirement of 125 staff-years.

Pricing Under NIH CRADAs

The Technology Transfer Act does not grant federal agencies the authority to control prices of products developed under CRADAs. In fact, the NIH is the only government agency that asks its CRADA partners to sign a "reasonable pricing" clause. Perhaps for that reason, the language of the standard NIH "reasonable pricing" clause is very general. The Taxol CRADA is specifically worded to take into account the unusually short period of exclusivity before Bristol-Myers Squibb will be confronted with competition in the marketplace.

There are at least three ways in which the NIH can properly constrain a collaborator's discretion to set prices:

* If the NIH has serious concerns as to whether a particular potential collaborator did not in the past, or will not in the future, act responsibly in the pricing of products developed under a CRADA, the agency can freely choose not to become involved in a research collaboration with that company.

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* The NIH can and should take action in cases in which there is clear evidence of irresponsible behavior, and has ample authority to ask the collaborator to explain its actions and to terminate the CRADA if the collaborator is unwilling or unable to do so.

* The NIH can and should encourage competition in the marketplace, so that market forces will act as a restraining influence on the prices of products developed under CRADAs.

Drug pricing is a complex process and requires detailed and ongoing analysis of a wide range of factors including direct and indirect research costs, raw material production costs, size and characteristics of potential markets, existing and anticipated competition, the nature and extent of patent rights, lost opportunity costs, the policies of third-party payers and the cost of the indigent patient programs.

In testimony before a congressional committee, Reid Adler, director of the NIH Division of Technology Transfer, noted that several companies have already declined to become involved in important collaborative research projects because of concerns about the impact of "reasonable pricing" clauses.

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Other companies can be expected to withdraw from the process as well, if the NIH adopts a policy that favors the use of pricing clauses to set prices or to impose burdensome requirements on collaborators with respect to the submission of confidential financial information in support of the prices that have been established.

How CRADAs Benefit the Public

CRADAs are intended to promote development of new products and processes for public benefit. When NCI gave Taxol its highest priority status in 1989 and advertised for a CRADA partner, it had reached a point where it needed a commercial partner to expedite the drug's development and make it available to the public.

Public benefits of this government/industry partnership are enormous. Taxol has received FDA approval far sooner than anyone expected, making this important drug available to thousands of women who may benefit. Also, success in finding alternative sources of Taxol means that reliance on bark will end sooner than expected.

The concept of the CRADA is simple and remarkably sensible. By combining the most valuable capabilities and resources of government and private industry, scientific research becomes practical reality and everyone benefits.

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It is important that future CRADAs not be threatened by politicizing pricing. Active government regulation of CRADA product prices may appear to control costs, but, instead, it could cost patients access to important new drugs.

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12/29/92

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CHRONOLOGY OF TAXOL® DEVELOPMENT

1958	The National Cancer Institute (NCI) initiated a long-term program that screened 35,000 plant species for anticancer activity.
1962	As part of the NCI screening program, the U.S. Forest Service collected Pacific yew bark, needles and twigs, and sent this raw material to the NCI for study.
Late 1960s	Samples of the collected materials were used to test for anticancer activity. Substances in the yew samples showed some anticancer activity.
1971	Drs. Monroe Wall and M. C. Wani of Research Triangle Institute, North Carolina, first identified paclitaxel as the active ingredient of the bark extract from the Pacific yew tree. Further development of paclitaxel was suspended for more than a decade due to the lack of evidence of superior activity in available experimental models, and problems with procuring, extracting and processing the compound.
1979	Susan Horwitz, Ph.D., at Albert Einstein College of Medicine in New York, identified paclitaxel's unique mechanism of action. She noted that paclitaxel prevents cells from dividing by promoting the assembly but inhibiting the disassembly of microtubules (the fibrous skeletal structures which assemble and divide throughout a cell's life.)
1983	NCI began screening and toxicological studies on Taxol and started Phase I clinical trials studying the drug for possible use with numerous cancer types. Initial clinical results were mixed. Allergic reactions attributed to the solvent used in formulating Taxol caused some trials to be discontinued and others delayed.

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1985	Phase II clinical trials began.
1989	Researchers at Johns Hopkins Oncology Center reported a 30 percent response rate in patients with advanced ovarian carcinoma who received Taxol. The results intensified NCI's interest in Taxol, but supply shortages hindered progress.
Aug. 1989	**NCI announced it would seek a commercial partner to aid in the** development of Taxol. It advertised for applications in the Federal Register, inviting pharmaceutical companies to compete for the rights to be its commercial development partner for Taxol. Approximately 20 companies requested information in response. Only four submitted proposals.
1990	Phase III clinical trials began.
Jan. 1991	NCI and Bristol-Myers Squibb signed a Cooperative Research and Development Agreement (CRADA) designed to speed the development of Taxol. Bristol-Myers Squibb was selected based on the Company's 30-year history in oncology drugs, its considerable resources and infrastructure, its expertise and the aggressive plan it submitted for Taxol's development. The CRADA stipulated that NCI would provide the Company with exclusive rights to clinical and pre-clinical data needed to submit a New Drug Application (NDA) seeking approval to market Taxol in the United States. In return, Bristol-Myers Squibb would increase the supply of yew bark and formulated Taxol available to the NCI; would initiate a search for alternative sources; and would file a NDA within four years. Bristol-Myers Squibb immediately made Taxol its top research priority at the expense of other projects.
June 1991	The Secretaries of Health and Human Services, Agriculture and Interior signed a Memorandum of Understanding pledging that all three departments would work together to support the Taxol development project. Bristol-Myers Squibb entered into separate 5-year cooperative agreements with the U.S. Forest Service and Bureau of Land Management to obtain Pacific yew bark from federal lands to support Taxol production.

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Sept. 1991	NCI began a Treatment Referral Center program for ovarian cancer patients whose chemotherapy had proven ineffective.
1991	Bristol-Myers Squibb provided the NCI with 1.35 kilograms of Taxol, more than twice the amount NCI obtained in the previous year -- and a third more than the target set by the CRADA.
1991	Bristol-Myers Squibb signed agreements with more than a dozen outside organizations to provide for the fastest possible development of alternative sources of Taxol.
Jan. 1992	Bristol-Myers Squibb increased its delivery of Taxol to the NCI from 5,000 vials per month to 25,000 vials per month.
April 1992	Bristol-Myers Squibb increased its delivery of Taxol to the NCI from 25,000 vials per month to 50,000 vials per month. This volume of Taxol was 30 times that obtained by NCI in 1990 -- the year before the CRADA was signed.
July 1992	Congress passed the Pacific Yew Act of 1992 to help ensure a steady supply of Pacific yew from federal lands while alternative sources are being developed and to ensure long-term preservation of the Pacific yew.
	Bristol-Myers Squibb filed a NDA for Taxol, just 18 months after entering into the CRADA.
	The company also relinquished orphan drug status for Taxol -- even though the drug qualifies for the designation -- because Bristol-Myers Squibb believes the potential use of Taxol for ovarian cancer and other tumor types would place it outside the spirit and intent of the Orphan Drug Act.
Oct. 1992	NCI began a Treatment Referral Center program for advanced breast cancer patients whose chemotherapy was no longer effective.

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Nov. 1992	The Food and Drug Administration Oncologic Drugs Advisory panel recommended that Taxol be approved for treatment of refractory ovarian cancer.
Dec. 1992	The U.S. Food and Drug Administration cleared Taxol for treatment of patients with ovarian cancer whose first-line or subsequent chemotherapy has failed.

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BRISTOL-MYERS SQUIBB CRADA ACHIEVEMENTS

Agreement with National Cancer Institute signed January, 1991.

	OBJECTIVE	ACHIEVEMENT
1.	Gather 750,000 lbs. of Pacific yew bark.	BMS collected more than 825,000 lbs. of bark, half from federal lands and half from private lands, in 1991.
2.	Provide 1 kilogram formulated Taxol to NCI in 1991.	BMS delivered 1.35 kilograms of Taxol of Taxol to NCI in 1991. In 1992, BMS increased supplies from 5,000 to 25,000 vials per month in January, and to 50,000 per month in April -- the equivalent of over 16 kilograms in 1992.
3.	Increase Taxol supply for NCI NCI clinical trials. Before the CRADA, the available amount of Taxol could treat an average of 500 patients per year.	BMS has supplied NCI with enough Taxol to treat an average of 8,000 to 10,000 patients in 1992.
4.	Initiate a search for alternative sources with the goal of ending yew bark reliance in 5-8 years.	BMS has accelerated its plan to reduce reliance on yew bark. Before the end of 1993 it will produce significant amounts of Taxol using semi-synthesis and will file a SNDA for commercial use of this method In 1994, BMS expects to use bark for less than half the total Taxol requirement and to use only small amounts of bark in 1995.
5.	File a New Drug Application within four years.	BMS filed an NDA July 22, 1992, 18 months after the CRADA was signed.

In only two years, BMS has invested several times the government's expenditures -- far in excess of the CRADA requirement of $114 million -- and 205 staff years to bring Taxol to market. The government has spent $23 million on Taxol in over 30 years.

345 Park Avenue New York, NY 10154-0037 Pharmaceuticals Consumer Products Nutritional Products Medical D

Bristol-Myers Squibb Company

News

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DEVELOPING ALTERNATIVE SOURCES OF TAXOL®: BACKGROUND INFORMATION

According to the National Cancer Institute (NCI), Taxol® (paclitaxel) is one of the most important anticancer drugs developed in the past decade. Although Bristol-Myers Squibb and its research partners have made significant progress in developing alternative sources of Taxol, the bark of the Pacific yew tree is currently the only approved source of Taxol for human use.

To expedite the development of Taxol, NCI signed a Cooperative Research and Development Agreement (CRADA) with Bristol-Myers Squibb Company in January, 1991 after a competitive process involving several pharmaceutical companies. The agreement stipulates that, in exchange for exclusive access to NCI clinical and pre-clinical data necessary to file a New Drug Application, the company will supply Taxol to NCI for clinical research and compassionate use programs, investigate alternative sources of Taxol and file a New Drug Application for Taxol as quickly as possible.

Bristol-Myers Squibb has exceeded all goals established in the CRADA and has made progress in developing alternative sources much more rapidly than initially thought possible.

The company has been conscious from the beginning of the nonrenewable nature of Pacific yew bark as the primary source of the drug and has been determined from the outset to find alternatives.

Bristol-Myers Squibb originally projected in 1991 being able to end reliance on Pacific yew bark within five to eight years. At the December, 1992 press conference announcing FDA clearance to market Taxol, company officials reported that significant amounts of Taxol will be produced by semisynthetic means in 1993, and that Bristol-Myers Squibb expects to eliminate the need for Pacific yew bark completely by the end of 1995 -- essentially accomplishing this objective in half the time originally anticipated.

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The company continues to conduct research in its own laboratories and is supporting multiple, simultaneous research programs around the world to develop additional alternative sources. Millions of dollars have been committed to the effort and more than a dozen agreements have been reached with various companies, researchers and academic institutions.

RESEARCH PROGRAMS

Following are specific programs supported by Bristol-Myers Squibb in its comprehensive search for alternative sources.

I. SEMI-SYNTHESIS

The most promising alternative source, and the alternative expected to produce significant amounts of Taxol in 1993, is semi-synthesis. This method produces Taxol from a precursor, 10-deacyl-baccatin III (10-DAB), which comes from entirely different yew species, the European Taxus baccata and the Himalayan Taxus wallichiana.

Bristol-Myers Squibb has reached an agreement with Indena -- a company in Milan, Italy which specializes in natural products -- under which Indena will extract 10-DAB, the Taxol precursor, from the twigs and needles of these trees. As a source of Taxol, twigs and needles offer a considerable advantage over bark, since they are renewable biomass.

Bristol-Myers Squibb has licensed methods being perfected by Robert Holton, Ph. D., at Florida State University in Tallahassee to convert 10-DAB into Taxol and continues to support Dr. Holton's research efforts to improve the process further.

II. YEW CULTIVATION

As indicated above, Taxol has been found in other Taxus species around the world. Another source under study is development of a domesticated alternative to wild population Pacific yew through the use of commercial plantations.

Bristol-Myers Squibb signed a three-year research agreement with Weyerhaeuser Company in August, 1991 to determine the best species to cultivate. Methods to enhance the seedlings' growth rate and their content of Taxol or its precursor are also being studied.

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Since cultivated biomass is required before this research will be completed, over five million seedlings of a readily available ornamental yew have been planted already and will be ready for harvest in 1994. Subsequent crops should be enhanced by results of the research in progress, and Weyerhaeuser currently has more than 20,000 yew trees in research trials.

Investigators at the University of Mississipi's Research Institute of Pharmaceutical Sciences are working under a separate agreement -- in collaboration with the Ohio Agricultural Research and Development Center and Zelenka Nursery -- to investigate the use of raw materials from ornamental yew nursery stock clippings as a source of Taxol.

Other research supported by Bristol-Myers Squibb into various ornamental and wild yew species as potential sources of Taxol includes research at the New York Botanical Gardens and the State Pharmaceutical Administration of China.

III. PLANT CELL CULTURE

To date, no pharmaceutical products are produced on a commercial scale by plant cell culture techniques. However, researchers have found it possible to grow cells in the laboratory from yew tissues, and then to use the cells to produce small quantities of Taxol.

Bristol-Myers Squibb is exploring this approach and is encouraged at this early stage by the control, adaptability and potential similarity to well-established fermentation and mammalian cell culture production techniques. Researchers are working to make this process, which is currently very lengthy, commercially feasible.

Bristol-Myers Squibb has established a research and development collaboration with Phyton Catalytic, Inc. -- a plant biotechnology company based in Ithaca, N. Y. -- to develop a plant cell tissue culture process for the production of Taxol. Phyton Catalytic was the first commercial organization to produce Taxol in a tissue culture system and has an exclusive license from the U.S. Department of Agriculture to produce Taxol using this technology.

Bristol-Myers Squibb is also constantly examining research under way at a variety of academic institutions, such as the work being conducted at Pennsylvania State University on the development of improved cell lines for the plants that produce Taxol.

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IV. TOTAL SYNTHESIS

The complexity of Taxol's chemical structure has thus far prevented researchers from totally synthesizing the Taxol molecule despite the efforts of many academic laboratories. But researchers are making significant progress and believe total synthesis could someday provide a reliable source of Taxol that is not dependent on any natural product.

Bristol-Myers Squibb is currently sponsoring well-advanced research at Ohio State University by Dr. Leo Paquette and at Stanford University by Dr. Paul Wender. The Stanford research team has discovered it is possible to make a core molecule like that found in Taxol from a pine tree extract, pinene, which is a major component of industrial solvents such as turpentine and thus readily available. Additional work is required to complete this phase of research and to develop it to a level where it will be commercially viable, a process that could take several years.

At Ohio State, researchers sponsored by Bristol-Myers Squibb began a two-year research program in August, 1991. They are attempting to assemble the framework of the Taxol molecule to create synthetic Taxol. Although initial progress has been promising, the final stages of the project are still not imminent.

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BACKGROUND: THE PRICING OF TAXOL

Bristol-Myers Squibb Company has thoroughly evaluated a number of factors in determining the price of Taxol® (paclitaxel). First, Bristol-Myers Squibb has carefully considered the government's investment in Taxol research and development and has taken that investment into account in establishing the price. Second, the Bristol-Myers Squibb corporate philosophy of fair and responsible pricing includes a goal of providing universal access to life-saving medications such as Taxol regardless of the patient's ability to pay. The inclusion of Taxol in the Bristol-Myers Squibb Oncology Access Program, the establishment of lower Medicaid and Federal Supply Schedule prices, and the provision of free product to the National Cancer Institute all reflect a commitment to this goal. As a result, the net effective weighted average cost for Taxol is expected to be approximately 30% below the wholesale list price. Importantly, no patient will be denied this drug because she does not have the means to pay for it.

On the other hand, Bristol-Myers Squibb must recover its investment in Taxol and return a profit to its stockholders. In two short years, the company has devoted financial and human resources to the development of Taxol which far exceed the Collaborative Research and Development Agreement (CRADA) goals of $114 million and 125 staff years. Bristol-Myers Squibb will continue this extensive resource commitment for the foreseeable future by aggressively pursuing alternative sources of Taxol and by conducting clinical research designed to define the optimum dosage and administration schedule and to explore the role of Taxol in combination chemotherapy, first-line treatment of ovarian cancer, and the

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treatment of other tumor types. The company will also support any extensive medical education designed to ensure appropriate Taxol use. While Bristol-Myers Squibb has made an extraordinary investment in Taxol, the compound lacks the patent protection typically available to new pharmaceutical products. As a result, the company will have only five years of exclusivity before potential competition from generic paclitaxel products, and competitive taxane analogues such as Taxotere are projected to be approved within the next two years.

Additional important considerations taken into account in determining the price of Taxol were high raw material costs, the extremely complicated and expensive production process, and the limited indication -- refractory ovarian cancer -- for which Taxol will initially be approved.

Bristol-Myers Squibb believes that the pricing structure for Taxol outlined below fairly and accurately reflects each of these important factors.

Taxol Pricing Structure

Method of Distribution	Price Per 30 mg Vial
Wholesale	$146.10
Physician Direct	140.26
Medicaid (after rebate)	123.16
Federal Supply Schedule (after discount)	108.11
Public Health Service (after discount)	123.16
NCI Clinical Supply	No Charge
Treatment Referral Center Protocols	No Charge
BMS Oncology Access Program	No Charge

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1Taking into account the range of prices associated with different methods of distribution, the net effective weighted average cost of Taxol per vial is expected to be approximately $103. The projected cost per cycle of Taxol therapy at this net effective weighted average cost is $695.25. At the wholesale list price of $146.10 per vial, which is the highest of the prices Bristol-Myers Squibb will charge for Taxol, the projected cost per cycle of therapy in the treatment of refractory ovarian cancer is $986.18.

Despite the huge investment, high production costs, and limited period of exclusivity associated with Taxol, the projected cost per cycle of Taxol is well below that of many other recently-approved cancer therapy agents and is in the mid-range of other agents currently used in the treatment of refractory ovarian cancer.

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FOR IMMEDIATE RELEASE

BRISTOL-MYERS SQUIBB ANNOUNCES TAXOL PATIENT ACCESS AND REIMBURSEMENT ASSISTANCE PROGRAMS

NEW YORK, N.Y. (December 29, 1992) -- Bristol-Myers Squibb Company today announced two programs to ensure that patients with limited financial resources for whom the newly approved anticancer drug Taxol® (paclitaxel) is prescribed can obtain it. The Taxol Patient Access Program and the Taxol Reimbursement Assistance Program were announced in conjunction with the company's announcement that the U.S. Food and Drug Administration has cleared Taxol for use in treating patients with ovarian cancer whose first-line or subsequent chemotherapy has failed.

The Taxol Patient Access Program

"We are very pleased to announce establishment of the Taxol Patient access Program," said Isadore M. Pike, M.D., Medical Director, Bristol-Myers Oncology Division. The program will provide Taxol free of charge to patients who are not insured or eligible for government assistance and who lack the ability to pay. "It is our intent that no patient be denied Taxol because she is unable to pay for it," said Dr. Pike.

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The Taxol program is the latest addition to the Bristol-Myers Squibb Oncology Access Program. Through this program, which began in 1973, the company provides its anticancer agents at no charge to eligible patients.

"We are expanding the effort significantly today by adding Taxol to a list that already includes all 13 of our company's other cancer-fighting agents," said Dr. Pike. He indicated that more than 8,500 patients have benefitted from the Bristol-Myers Squibb Oncology Access Program in the past five years alone.

Eligible patients can become part of the Taxol Patient Access Program through their physicians. Physicians can call 1-609-897-2128 weekdays from 8 a.m. to 5 p.m. EST for additional information.

Taxol Reimbursement Assistance Program

The Taxol Reimbursement Assistance Program is designed to help physicians obtain coverage for their patients from third-party payers.

"There are numerous government, nonprofit and private sources of reimbursement for cancer therapy and it is sometimes very difficult for physicians to know where to turn for the help they seek for their patients," said Dr. Pike.

A Taxol Reimbursement Assistance HelpLine with a toll-free number has been established and is staffed by information specialists trained to help physicians work with private and government insurers to obtain coverage for their patients.

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The toll-free number, which is for use only by physicians in the U. S., is 1-800-872-8718. Calls are answered from 9 a.m. to 5 p.m. (EST) every weekday; at other times calls are recorded and returned on the next business day.

The company also said that ovarian and breast cancer patients who are being treated with Taxol by the National Cancer Institute through the NCI Treatment Referral Center Program will continue to receive it free of charge for as long as their physicians deem necessary.

Bristol-Myers Squibb is a diversified, research-based health care company whose principal businesses are pharmaceuticals, consumer products, nutritionals and medical devices.

# # #

TAXOL® (paclitaxel):

KEY CONSIDERATIONS IN DETERMINING A FAIR AND RESPONSIBLE PRICE

Date: December 3, 1992

I. Background

The development of TAXOL® (paclitaxel) has been a 30-year quest, filled at times with seemingly insurmountable challenges. Through the perseverance of independent researchers, the resolve of the National Cancer Institute (NCI), and the collaboration of Bristol-Myers Squibb (BMS), TAXOL is finally nearing commercial availability. The efforts of these groups have overcome a number of substantial obstacles in the development of TAXOL as a safe and effective chemotherapeutic agent, including a difficult purification scheme, poor solubility, and a limited source of drug supply.

TAXOL was discovered through an NCI-sponsored program which screened 35,000 plant species for anticancer activity between 1958 and 1980. In 1971, Monroe Wall and M.C. Wani of the Research Triangle Institute first identified TAXOL as the active moiety of the bark extract from the Pacific Yew tree. Further development of TAXOL was suspended for more than a decade, however, due to the lack of evidence of superior activity in available experimental models, and the problems associated with procurement, extraction, and processing of the product.

In 1979, interest in TAXOL was rekindled when Susan Horwitz and co-workers at Albert Einstein discovered the unique mechanism of action of the product.

Phase I clinical studies of TAXOL began in 1983, but were slow to develop. Hypersensitivity reactions attributed to the Cremophor® EL (polyoxyethylated castor oil)[1] vehicle delayed the completion of many Phase I trials, and led to the discontinuance of others. Also, because of ongoing manufacturing difficulties, ensuring adequate supplies for clinical trials was a constant problem.

Eventually, Phase II trials in melanoma, renal cell carcinoma and ovarian cancer were cautiously opened. In 1989, enthusiasm for TAXOL grew when McGuire and co-researchers from Johns Hopkins reported a 30% response rate in patients with advanced ovarian carcinoma. This report inspired efforts to broaden clinical investigations of TAXOL but a limited supply of the product continued to restrict the breadth of clinical studies.

In late 1990, NCI entered into a Collaborative Research and Development Agreement (CRADA) with BMS. The purpose of this CRADA is to conduct collaborative research on the development of TAXOL as an antitumor agent, and to generate data necessary to obtain FDA approval for this compound.

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[1] Cremophor EL is the registered trademark of BASF Aktiengesellschaft.

The CRADA was awarded following a full and open competition, including publication in the Federal Register, and a thorough scientific review by government scientists of the proposals submitted. Four companies responded to the request for applications, and in the judgement of NCI, BMS was clearly the most qualified because of its extensive experience in the development of anticancer drugs and its commitment to quickly bring TAXOL to final new drug application status.

II. BMS Responsibilities Under the CRADA

BMS had three primary responsibilities under the CRADA, as follows:

1. Supply TAXOL to the NCI
2. Establish alternative source(s) of supply to the Pacific Yew bark
3. Commercialize TAXOL

Recognizing the importance of these responsibilities, BMS established four very broad, ambitious goals, which some initially considered unrealistic. Yet, just one year after the signing of the CRADA, all four goals were exceeded.

III. BMS Goals

A. Increase Supplies of Pacific Yew Bark

The first BMS goal was to collect 750,000 pounds of Pacific Yew bark during the first year of the CRADA. This target was dramatically higher than actual levels produced in prior years. To help accomplish this goal, BMS entered into collaborative agreements with the National Forest Service (NFS) and the Bureau of Land Management (BLM). Throughout this intensified harvest effort, BMS has paid the administrative costs incurred by both agencies in connection with Pacific Yew bark transfer, has underwritten the costs of preparing a Pacific Yew inventory, conservation guidelines and related environmental documents (including a comprehensive, programmatic environmental impact statement), and has supported research on the management and preservation of the Pacific Yew. As a result, approximately 825,000 pounds of bark were collected in 1991 and an equal amount was collected in 1992, which was substantially in excess of the goal. During this two-year period, approximately equal amounts of bark were collected from federal and private lands.

B. Increase Supplies of TAXOL

The second goal was to increase quantities of TAXOL so that the NCI could conduct an increasing number of clinical trials. Prior to the signing of the CRADA, the NCI obtained an average of 0.5 kilograms of TAXOL per year, or enough to treat only several hundred patients per year. BMS agreed to double that amount during the first year of the CRADA. Ambitious as it was, this target was exceeded. Just three months after the CRADA was signed, BMS began shipments of TAXOL to the NCI. By the end of 1991, 1.35 kilograms of bulk drug, or 45,000 vials, had been delivered. In January 1992, supply was increased from 5,000 vials per month to 25,000 vials per month, and by April 50,000 vials per month were being provided at no charge to the NCI. This was the equivalent of 16 kilograms of TAXOL per year -- and enough drug to treat nearly 10,000 patients annually. Thus, in a two year period, BMS increased the clinical supplies of TAXOL available to the NCI more than 30-fold.

C. Initiate Search for Alternative Sources of TAXOL

While expansion of TAXOL production from bark was an immediate imperative, BMS recognized that bark was a finite source. As a result, the company began an aggressive program to identify alternative, long-term, commercially viable TAXOL supply sources with the objective being to significantly reduce or eliminate dependence on bark within three to five years. In addition, BMS is pursuing improved bark derivatives. Through a comprehensive effort involving agreements between BMS and numerous other organizations (see Appendix 1), four areas are proving to be particularly promising alternatives: precursor isolation and semi-synthesis, yew cultivation for biomass production, plant cell culture, and total synthesis.

Semi-synthesis

The company entered into an agreement with Indena, an Italian company specializing in research and production of botanical derivatives. This agreement will provide for large quantities of a TAXOL precursor (Baccatin III) from renewable biomass (needles and twigs), which will be used to produce TAXOL through a semi-synthetic process licensed from Florida State University. Significant quantities of TAXOL are expected to be manufactured from this process as early as 1994.

Yew Cultivation

BMS has entered into a contract with Weyerhauser Company, one of the largest forest product companies in the world, to determine the best species of yew for cultivation of biomass for TAXOL production. More than 5 million seedlings of a readily available ornamental cultivar have already been planted. These yew plantations will provide an ongoing supply of biomass beginning in late 1994. Also, BMS has entered into an agreement with the University of Mississippi to explore the feasibility of using ornamental yew nursery stock clippings.

Plant Cell Culture

To date, no pharmaceutical products are produced on a commercial basis using plant cell culture techniques. BMS is exploring this area in collaboration with Phyton Catalytic, Inc., a plant biotechnology company, and through an agreement with researchers at Pennsylvania State University.

Total Synthesis

Due to the complexity of the TAXOL molecule, total synthesis will be extraordinarily difficult. BMS, however, is sponsoring efforts in this regard with researchers at Ohio State University and at Stanford University. Significant progress has been reported by both investigators.

D. File an NDA within Four Years

The final CRADA objective for BMS was to file a New Drug Application within four years after the CRADA was signed. Through an accelerated, massive investment of financial and human resources which made TAXOL the top corporate priority of BMS at the expense of other key projects within the Company, BMS was able to file an NDA on July 22, 1992 -- two and one-half years earlier than the CRADA goal. Barring unexpected delays by the FDA, TAXOL could be approved and made available for general clinical use in the United States only two years after the CRADA was signed.

Appendix 2 contains a more detailed listing of BMS performance versus these and other specific CRADA objectives.

IV. Pricing Philosophy

The Bristol-Myers Squibb pricing philosophy is founded on the belief that "fair and responsible pricing" should be provided to all segments of the prescription drug marketplace. BMS maintains that responsible pharmaceutical pricing should achieve the following balance:

> ***The pricing structure of a new drug must provide adequate funds to repay the enormous research investment required to bring the product to market and thereby, return a profit to the stockholders, yet include provisions to ensure the drug will be available to all who need it.***

There is considerable evidence of the commitment BMS has made to this philosophy.

A. New Product Introductions

Products in a broad range of therapeutic categories have recently been introduced by BMS, including VIDEX® (didanosine, ddI), for the treatment of AIDS; Monopril® (fosinopril sodium), a pharmaceutically improved ACE inhibitor for the management of hypertension; Pravachol® (pravastatin sodium), a hydrophilic HMG CoA reductase inhibitor that lowers serum cholesterol; and Cefzil® (cefprozil), an oral cephalosporin antibiotic with a broad spectrum of activity. Each of these products were priced below the market level at launch.

B. Lower Prices to Government Agencies

Lower prices are also provided to government agencies as stipulated in the "Omnibus Budget Reconciliation Act of 1990" and the "Veterans Health Care Act of 1992." For TAXOL, the price to state Medicaid programs will be 15.7% less than the wholesale direct (list) price, and the price to the Federal Government under the Federal Supply Schedule (FSS), will be 24% less than list. These special prices will allow the government at both levels to serve those in most need.

C. Indigent Patient Program

BMS has a strong history of making pharmaceutical products accessible to those in need through its Indigent Patient Program. For instance, since 1973, the Bristol-Myers Oncology Division has provided all of its anticancer drugs, at no cost, to any patients who cannot otherwise afford them. During the last five years, this program has fulfilled more than 16,000 patient requests for free product. TAXOL will be included in this program immediately at launch.

D. Support of NCI Clinical Studies

BMS will continue to provide TAXOL, at no charge, for those patients enrolled in NCI clinical studies prior to FDA approval, and those patients involved in future NCI clinical studies approved by the Joint Steering Committee under the CRADA. The NCI currently projects that more than 5,000 patients receiving TAXOL in the United States next year will receive the product free of charge through this program.

As evidenced by the above, a central element of the BMS pricing philosophy is the provision for **universal patient access** to all segments of the prescription drug marketplace, particularly for life-saving medications.

The price of TAXOL is being developed within the guidelines set forth in this philosophy providing for fair and responsible pricing; therefore, the price of TAXOL will address the needs of patients in all categories, while recognizing the uniqueness of this drug, the government's role in its discovery and development, and the enormous investment made by Bristol-Myers Squibb in its development.

V. Key Considerations in Determining the TAXOL Pricing Policy

A. Limited Exclusivity

The period of time that BMS will have to recover its investment before TAXOL faces competition will be much shorter than is normally the case for a new pharmaceutical product. Competition will come in at least two forms - analogues and generics - and is a near-certainty in the next several years.

The most imminent competition to TAXOL is Taxotere, a patented semi-synthetic TAXOL analogue under development by Rhone-Poulenc Rorer (RPR). RPR entered into a CRADA with the NCI earlier this year and the NCI is vigorously supporting the development of this and other potential competitors to TAXOL. FDA approval of Taxotere is anticipated within 18 - 24 months.

In addition, near-term generic competition for TAXOL is a certainty because TAXOL is not a patented product. This absence of patent protection means that BMS only has protection against Abbreviated New Drug Application (ANDA) filings for five years from the date of approval as provided under the Hatch-Waxman Act. While TAXOL qualified for Orphan Drug status as a treatment for refractory ovarian cancer, BMS believed that the potential utility of TAXOL could place it outside the spirit and intent of the Orphan Drug Act. Therefore,the Company voluntarily relinquished TAXOL Orphan Drug status, thereby giving up 7 years of exclusivity against full NDA's and an additional two years of exclusivity against generics that Orphan Drug Status would have provided. (This is a similar rationale to that underlying the decision by BMS to voluntarily relinquish Orphan Drug status for its anti-AIDS drug, VIDEX.) Recent reports indicate that the development of generic forms of TAXOL is already underway.

B. Government Investment

BMS is highly sensitive to the CRADA provisions specifying that careful consideration be given to the public's investment in TAXOL research and development. By the NCI's most recent estimate, government expenditures for TAXOL research and development will have reached approximately $32 million on a fully allocated basis. The NCI was instrumental in the drug discovery process with TAXOL and has played a key role in coordinating and facilitating the completion of clinical research on the drug. The full range of public investment and contributions to the development of TAXOL will be reflected in the price of TAXOL when it is established.

C. BMS Investment to Date

As noted above, the pricing of TAXOL will take into account the public investment in its development. Similarly, the price of TAXOL must reflect BMS's contribution of resources in the development of this important agent.

Since signing the CRADA, BMS has made massive investments of capital and manpower to provide adequate clinical supplies, research alternative sources, secure supply agreements and prepare the NDA for submission. A BMS commitment of up to $114 million and approximately 125 staff years to develop TAXOL was projected in the CRADA. BMS has already greatly surpassed these commitments, both in terms of the dollars and staff years invested.

Due to the urgency associated with getting TAXOL to patients as rapidly as possible, TAXOL became the number one research and development priority within BMS immediately after the CRADA was signed and has remained so since that time. As a result, key scientific personnel and resources have been pulled away for other important projects within BMS to expedite TAXOL development during the past two years. The opportunity cost associated with the diversion of resources away from other important BMS projects in support of TAXOL has been substantial.

D. Complex and Expensive Production Process

1. Current Method

While production of nearly all cancer chemotherapeutic agents is more complex than production of other types of pharmaceutical products, TAXOL is even more complex and time-consuming to produce. An appreciation for the complexity of this process can be obtained by comparing it to the production process employed for Platinol (cisplatin), another oncology product commercialized through the joint efforts of BMS and the NCI. A comparison of the general nature of the two processes is shown in Appendices 3 and 4. As shown in Appendix 3, cisplatin is derived from an expensive, yet known and readily available source of raw material that is consistent from batch to batch. Ten kilograms of raw material are needed to produce one kilogram of active bulk drug substance. The production process involves primarily standard pharmaceutical chemistry and requires the limited use of organic solvents. The number of steps involved in drug substance processing and drug formulation is similar to that of other "traditional" cancer chemotherapeutic agents. The total process from beginning to end requires approximately nine to ten weeks.

Appendix 4 shows a simplified version of the present production process that must be utilized for TAXOL. Raw material procurement is by itself a challenging proposition that takes approximately 22 to 28 weeks. The effort to obtain permits from the various land owners for access to harvest bark for one season begins as the previous one is ending. Obtaining permits is often a time-consuming and laborious process. The source of raw material for TAXOL, bark from the Pacific Yew tree, can only be harvested for 16-20 weeks each year. The bark is often difficult to procure and varies considerably in TAXOL content. Furthermore, the cost of procuring bark has increased nearly five-fold compared to earlier NCI procurement, primarily due to the costs associated with environmental safeguards and cooperative agreements with the United States Forest Service and the Bureau of Land Management. Between 7,000 and 10,000 kilograms of bark are often needed to yield just one kilogram of drug substance.

Drug substance processing for TAXOL is a complicated series of operations requiring nine steps that take approximately eight weeks to complete. This part of the manufacturing process requires the use of large volumes of organic solvents. Because TAXOL is derived from trees, drug substance testing involves the analysis of 28 separate parameters.

This testing takes twice the effort and requires significantly more manpower to complete than does the bulk drug testing required for cisplatin. Drug product formulation requires an expensive explosion proof facility in which to perform the four processing steps involved in this part of the process. In addition, a totally separate facility is needed for processing Cremophor. Finally, finished product testing involves 19 totally distinct parameters. The total process from beginning to end takes an average of 37 to 44 weeks.

In summary, the production method for TAXOL is a labor intensive, complicated, lengthy and expensive process even when compared to production processes utilized for other cancer chemotherapeutic agents. In fact, recent estimates by the NCI suggest that its costs associated with the production of non-commercial grade TAXOL 4-5 years ago were ten-fold higher than similar costs for cisplatin. Moreover, these figures do not reflect the nearly five-fold increase in the price of bark since that time, the enormous costs associated with commercial scale up and the production of TAXOL to more stringent FDA standards, or the substantial investments made in alternative sources.

2. Future Method

The evolving clinical significance of TAXOL may ultimately support its use in the treatment of a range of malignancies, including ovarian, breast, and non-small cell lung cancer. This potential increase in demand could put intolerable pressure on the Pacific Yew as the only source for TAXOL. Consequently, the commitment to commercialize TAXOL carried with it the requirement to expeditiously develop alternative, renewable sources.

Typically, in a project such as this, a range of alternatives would be identified, priorities would be set, and the most promising approaches would be explored in a sequential order. However, given the critical importance of developing viable alternative sources on a tight time-line and in keeping with the spirit of the CRADA, BMS proceeded on several fronts at the same time.

This expedited approach increased both the complexity and cost of this effort. Appendix 1, as mentioned previously, provides a listing of the major agreements into which BMS has entered to ensure alternative product sources. These parallel efforts are expected to result in the commercial availability of a renewable, semi-synthetic product as early as 1994, and the promise of several other innovative sources in 1994 and beyond. In addition, licensing and research efforts will continue well beyond FDA approval of TAXOL to insure that a variety of inexhaustible and environmentally agreeable sources are available.

E. Future BMS Investment

An extensive resource commitment will continue for the foreseeable future. Substantial support will be required for the research, development, plant and equipment necessary to bring alternative sources on-line as stipulated in the CRADA and to obtain FDA approval for using them to manufacture TAXOL for the commercial market.

Additionally, on-going studies will be necessary to fully characterize and realize the clinical potential of TAXOL. Although the NCI will continue to conduct intramural studies designed to address key clinical issues, an even greater burden of responsibility will shift to BMS after FDA approval. For example, BMS will commit substantial resources to exploring the role of TAXOL in combination chemotherapy, in front line settings, in combined modality therapy, in adjuvant settings and for studies to further define the appropriate dosage and administration schedule.

BMS commitment to educating health care professionals will be essential to ensuring the appropriate utilization of this drug. There currently exists a high level of general awareness in the oncology community regarding TAXOL, but a low level of knowledge about specific characteristics of the drug's profile. This is due primarily to the fact that very few oncologists have any direct clinical experience with TAXOL.

As an example of this information void, recent market research found that 99% of all oncologists surveyed were aware of TAXOL; however, only 25% of oncologists were very knowledgeable about this new agent. Areas where oncologists lack information at present include TAXOL response rates, mechanism of action, side effect profile, premedication requirements, dosage, administration, and use in combination with other chemotherapeutic agents -- all of which require complete and accurate elucidation prior to physicians adding TAXOL to their chemotherapy armamentarium. Furthermore, this education process will continue for some time to come. As discussed earlier, the clinical importance of TAXOL is continuing to evolve into front-line therapy, multi-agent regimens, and combined modality therapy, among others.

In response to these immediate and ongoing educational needs, BMS will expeditiously provide accurate, and up-to-date information to the entire oncology audience. This effort will require use of the entire Bristol-Myers Oncology Division organization including an expansion of the Medical Services Department.

In summary, BMS will continue to make an extraordinarily high investment in TAXOL over at least the next five years.

F. Product Use

The size of the patient population to be treated with TAXOL remains unclear. TAXOL was evaluated and submitted to the FDA for the treatment of patients with ovarian cancer who have failed standard treatment regimens. There are approximately 21,000 new cases of ovarian cancer diagnosed in the United States every year, only a portion of which fail first line chemotherapy and proceed to second line treatment. Approximately 12,500 deaths result from this condition yearly.

On November 16, 1992, the Oncologic Drugs Advisory Committee (ODAC) unanimously recommended to the FDA that TAXOL be approved for ovarian cancer patients failing first line chemotherapy or subsequent chemotherapy. If the FDA follows the ODAC recommendation, the population of patients who fall within the labelled indication would be limited.

While TAXOL is likely to have utility beyond refractory ovarian carcinoma, the granting of additional indications by the FDA for TAXOL is uncertain; therefore, the ability of BMS to evaluate or project the commercial potential of the drug beyond this limited patient population is equally uncertain.

G. BMS Provisions for Patient Access

As mentioned earlier, a central element of the BMS "fair and responsible" pricing philosophy is to ensure universal patient access to all segments of the prescription drug marketplace. The provisions for patient access mean that many of the TAXOL vials distributed by BMS will be sold at substantial discounts to the list price or will be provided to patients free of charge.

1. Government Prices

   Most of the TAXOL sold to the government will be purchased by either state Medicaid programs or Federal Government agencies under the FSS. The price to state Medicaid programs will be reduced by 15.7% from the list price (after a 2% discount is deducted from list), and the price to Federal Government agencies will be reduced by 24% (after a 2% discount from list) under the FSS.

2. NCI Product Support

   Even after TAXOL is approved for marketing by the FDA, BMS will continue to provide free product to the NCI. The free product will be provided to patients enrolled in NCI clinical studies prior to FDA approval, and in support of ongoing studies sponsored by the NCI. The NCI currently projects that more than 5,000 patients receiving TAXOL in the United States next year will receive the product free of charge through this program.

3. Indigent Patient Program

   As stated earlier, BMS has a long history of making of all its oncology products accessible to needy patients through the Bristol-Myers Oncology Division Indigent Patient Program. As soon as TAXOL is marketed by BMS, it will be available free of charge to indigent patients through this program. Patients can apply to this program through their attending oncologist. No patient that was certified indigent by their physician has ever been turned away.

As illustrated above, there is no one price for TAXOL. Instead, there will be essentially five prices during 1993: 1) the wholesale direct price, often referred to as the list price; 2) the physician direct price (5% less than list); 3) the Medicaid price (15.7% less than list); 4) the Federal Supply Schedule price (24.0% less than the non-federal list price); and 5) product provided at no charge to the NCI for clinical research and provided through the Bristol-Myers Oncology Division Indigent Patient Program.

When properly weighted, the net effective price of TAXOL for all vials distributed is expected to be approximately 70% that of the list (wholesale direct) price.

VI. Summary

Nearly two years ago, Bristol-Myers Squibb and the National Cancer Institute entered into a Collaborative Research and Development Agreement to expedite the development of TAXOL. The overall goal was to make this important new agent available to patients at the earliest time possible. The Company clearly recognizes the enormous responsibility accompanying its partnership with the NCI. As the leader in the field of oncology, BMS has a long-standing commitment to providing safe and effective products in the fight against cancer. As such, BMS has cast the full force of its experience and resources into accomplishing the goals as set forth in the CRADA. The results have been quite remarkable, with each target being surpassed, and TAXOL now nearing FDA approval for the treatment of refractory ovarian cancer only two years after the CRADA was signed.

BMS is carefully considering a multitude of factors in determining the price of TAXOL. First, BMS is highly sensitive to the CRADA provisions specifying that consideration be given to the government's investment in TAXOL research and development. Second, BMS's corporate philosophy of "fair and responsible" pricing has as a central element the provision for universal patient access, in particular for life-saving medications such as TAXOL. Several actions, including the indigent patient program, lower government prices, and free product to the NCI, demonstrate a responsiveness to this directive. The result of these programs means that the net effective price for TAXOL is expected to be approximately 70% of the most commonly quoted price, the wholesale direct or list price.

On the other hand, BMS must recoup the company's investment and return a profit to it's stockholders. First, in two short years, BMS has committed a dollar amount to the development of TAXOL many fold the amount contributed by the government over a thirty-year period. Second, BMS will continue to pour enormous resources, both financial and human, into the continued development of TAXOL, including the pursuit of alternative sources for drug substance. Third, because TAXOL does not have the patent protection typically available to new pharmaceutical products, BMS will have an extremely short period of time in which to recover its investment. Fourth, product costs are high and the company must work with a production process that is much more complicated and time-consuming than that used to manufacture other chemotherapeutic agents. Lastly, TAXOL is likely to be approved by the FDA for a limited indication. Since the granting of additional indications for TAXOL is uncertain, the ability of BMS to directly affect the commercial potential of TAXOL beyond this limited patient population is equally uncertain.

In conclusion, BMS is thoroughly evaluating all factors in its effort to determine a fair and responsible price for TAXOL and as has been the case with other recent BMS product introductions, is working to ensure that all patients, regardless of ability to pay, will have access to this potentially life-saving drug.

APPENDIX 1

TAXOL

External Agreements for Alternative Supply and Derivatives

Research Agreement	Nature of Agreement
Florida State University	Semisynthesis
Indena	Precursor Isolation
Weyerhaeuser	Cultivated Biomass Research
University of Mississippi	Ornamental Cultivars: Harvest & Extraction Research
State Pharm. Admin. of China (SPAC)	Other *Taxus* Species: Feasibility Study
Ohio State University	Total Synthesis
Stanford University	Total Synthesis
Phyton Catalytic, Inc.	Plant Cell Tissue Culture
Pennsylvania State University	Plant Cell Tissue Culture
Virginia Tech	Improved Derivatives
New York Botanical Garden	Improved Derivatives and Species Survey
University of Kansas	Improved Derivatives

APPENDIX 2

TAXOL

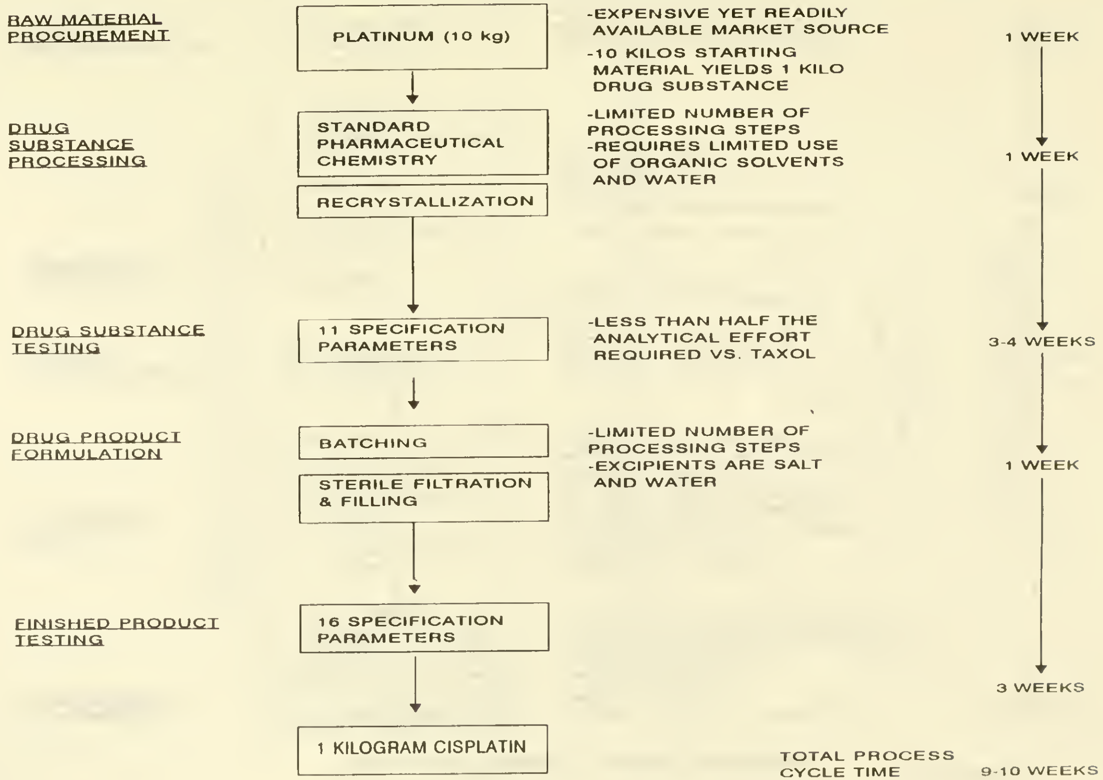
BMS/NCI TAXOL ACCOMPLISHMENTS

CRADA Objective	Current Status
BMS/NCI Joint Steering Committee	Established/Ongoing
BMS to commit $65-114 million in direct expenses for TAXOL development	Through 1992: Significantly exceeded commitment
BMS to commit 125 staff years to R&D	1991-92 est. staff yrs: 205
BMS/NCI to collaborate on design, oversight and implementation of clinical trials for FDA approval	Ongoing
BMS to initiate additional pre-clinical studies for drug registration	Number initiated: 17
BMS to collect all data from investigators	Ongoing
BMS to provide appropriate funds to investigators	Funds committed: $2.3MM
BMS to file NDA for refractory ovarian cancer within 4 years (Jan. 23, 1995)	Filed: July 22, 1992 (1 year, 6 months)
BMS to supply TAXOL for all current and future clinical trials or other research (per Steering Committee approval); includes compassionate use and Group C distribution	1991: 45,000 vials 1992: est. 525,000 vials
BMS to investigate and establish alternative source of TAXOL including: -other species of *Taxus* -partial or total synthesis -commercial propogation of *Taxus* -cell culture production	9 of 12 external agreements associated with alternate sourcing

AP2.TAX

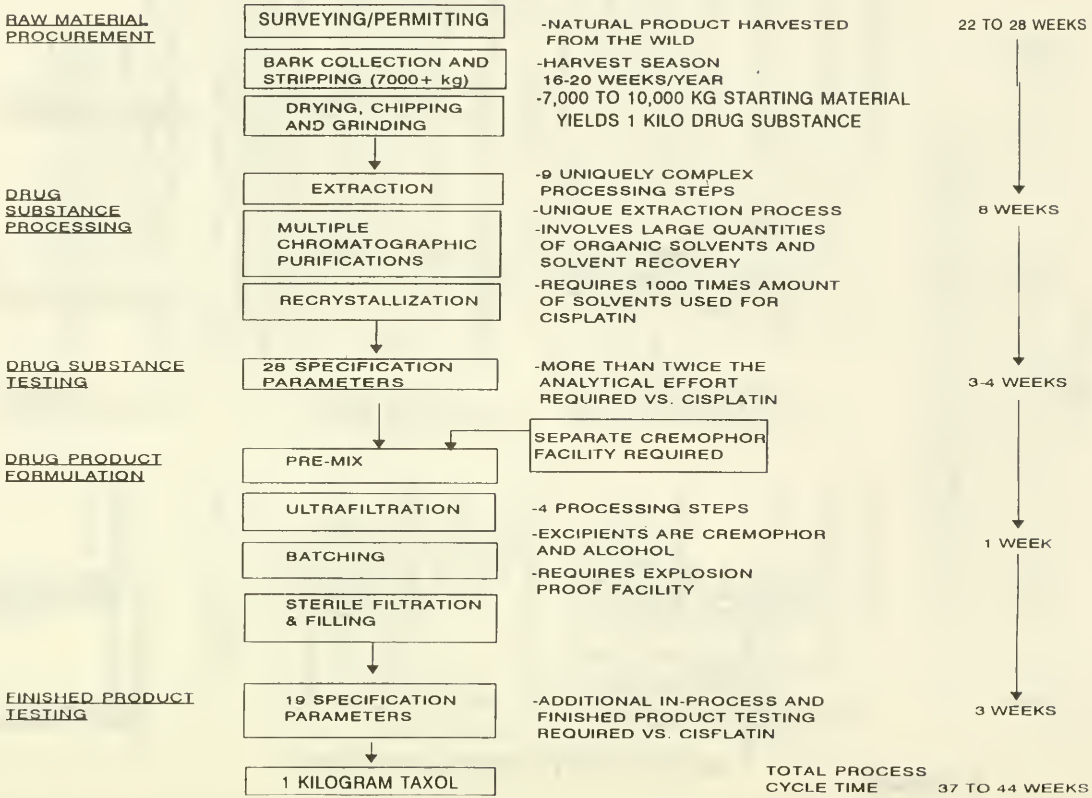
APPENDIX 3

CISPLATIN PRODUCT FLOW DIAGRAM


RAW MATERIAL PROCUREMENT
PLATINUM (10 kg)
-EXPENSIVE YET READILY AVAILABLE MARKET SOURCE
-10 KILOS STARTING MATERIAL YIELDS 1 KILO DRUG SUBSTANCE
1 WEEK
DRUG SUBSTANCE PROCESSING
STANDARD PHARMACEUTICAL CHEMISTRY
RECRYSTALLIZATION
-LIMITED NUMBER OF PROCESSING STEPS
-REQUIRES LIMITED USE OF ORGANIC SOLVENTS AND WATER
1 WEEK
DRUG SUBSTANCE TESTING
11 SPECIFICATION PARAMETERS
-LESS THAN HALF THE ANALYTICAL EFFORT REQUIRED VS. TAXOL
3-4 WEEKS
DRUG PRODUCT FORMULATION
BATCHING
STERILE FILTRATION & FILLING
-LIMITED NUMBER OF PROCESSING STEPS
-EXCIPIENTS ARE SALT AND WATER
1 WEEK
FINISHED PRODUCT TESTING
16 SPECIFICATION PARAMETERS
3 WEEKS
1 KILOGRAM CISPLATIN
TOTAL PROCESS CYCLE TIME
9-10 WEEKS

APPENDIX 4

TAXOL PRODUCT FLOW DIAGRAM


RAW MATERIAL PROCUREMENT
SURVEYING/PERMITTING
BARK COLLECTION AND STRIPPING (7000+ kg)
DRYING, CHIPPING AND GRINDING
-NATURAL PRODUCT HARVESTED FROM THE WILD
-HARVEST SEASON 16-20 WEEKS/YEAR
-7,000 TO 10,000 KG STARTING MATERIAL YIELDS 1 KILO DRUG SUBSTANCE
22 TO 28 WEEKS
DRUG SUBSTANCE PROCESSING
EXTRACTION
MULTIPLE CHROMATOGRAPHIC PURIFICATIONS
RECRYSTALLIZATION
-9 UNIQUELY COMPLEX PROCESSING STEPS
-UNIQUE EXTRACTION PROCESS
-INVOLVES LARGE QUANTITIES OF ORGANIC SOLVENTS AND SOLVENT RECOVERY
-REQUIRES 1000 TIMES AMOUNT OF SOLVENTS USED FOR CISPLATIN
8 WEEKS
DRUG SUBSTANCE TESTING
28 SPECIFICATION PARAMETERS
-MORE THAN TWICE THE ANALYTICAL EFFORT REQUIRED VS. CISPLATIN
3-4 WEEKS
DRUG PRODUCT FORMULATION
SEPARATE CREMOPHOR FACILITY REQUIRED
PRE-MIX
ULTRAFILTRATION
BATCHING
STERILE FILTRATION & FILLING
-4 PROCESSING STEPS
-EXCIPIENTS ARE CREMOPHOR AND ALCOHOL
-REQUIRES EXPLOSION PROOF FACILITY
1 WEEK
FINISHED PRODUCT TESTING
19 SPECIFICATION PARAMETERS
-ADDITIONAL IN-PROCESS AND FINISHED PRODUCT TESTING REQUIRED VS. CISFLATIN
3 WEEKS
1 KILOGRAM TAXOL
TOTAL PROCESS CYCLE TIME
37 TO 44 WEEKS

STATEMENT OF JAMES P. LOVE
Center for Study of Responsive Law
Director, Taxpayer Assets Project

before the
Subcommittee on Regulation, Business
Opportunities, and Energy

of the
Committee on Small Business
United States House of Representatives

on

PRIVATE SECTOR PRICING OF TAXOL AND OTHER PHARMACEUTICAL INVENTIONS DEVELOPED WITH FEDERAL FUNDING

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Introduction

Mr. Chairman and members of the Subcommittee, thank you for the opportunity to testify today on the topic of private sector pricing of pharmaceutical inventions that are developed with federal funding. The work of this Subcommittee and its staff have been instrumental in shedding light on a topic of grave importance to all health care consumers and taxpayers.

My name is James P. Love. I live in Ardmore, PA, where I am Director of the Center for Study of Responsive Law's Taxpayer Assets Project.[1] The Taxpayer Assets Project was started by Ralph Nader to investigate a wide range of issues related to the management and sale of government assets, including federally funded inventions and information resources. I have also held teaching and research positions at Princeton University, Rutgers University, and the National Bureau of Economic Research. From 1988 to 1990 I was Senior Economist for Russell-Zisler, a subsidiary of the Frank Russell Company, a large pension fund consulting firm.

I was a witness at the July 29, 1991 hearings held by this subcommittee which addressed many of the same topics that will be examined today.[2] My testimony at that hearing addressed our concerns about the National Cancer Institute's (NCI) Cooperative Research and Development Agreement (CRADA) with Bristol-Myers Squibb (BMS) for the development Taxol, as well as a more general critique of federal policies and practices regarding government funded medical research, such as the Federal Government's decision to extend Bristol-Myers' exclusive license to sell cisplatin, and the use of the Federal Orphan Drug Act to obtain monopoly marketing rights to highly profitable drug inventions, many of which were developed with federal funds.

Today I will revisit the question of Bristol-Myers Squibb's (BMS) Taxol CRADA, focusing particularly on the recently announced prices for Taxol, which were the result of negotiations between the company and NCI.

I will also provide general comments on broader issues relating to the pricing of government funded medical inventions, and make specific recommendations for policies and practices that will allow Congress, the Administration and the public to make informed decisions and exercise greater control over drug pricing in general.

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[1] In preparing for this testimony I was assisted by Michael Ward, a Research Associate of the Center for Study of Responsive Law.

[2] U.S. House of Representatives, Committee on Small Business, Subcommittee on Regulation, Business Opportunities and Energy, *Exclusive Agreements Between Federal Agencies and Bristol-Myers Squibb Co. for Drug Development: Is the Public Interest Protected?* July 29, 1991 hearings. Serial Number 102-35.

Taxol

On December 29, 1992 Bristol-Myers Squibb received FDA marketing approval for Taxol and the company immediately announced a wholesale price of $4.87 per milligram.[3] The issue before this Subcommittee is the reasonableness of that price.

Both NCI and BMS have given policy makers and the public the impression that Taxol is an expensive drug to manufacture. In fact, before BMS signed the Taxol CRADA, NCI had already developed the techniques for manufacturing the drug, and was able to obtain Taxol from contractors for about $.60 per milligram,[4] about one eighth the wholesale price announced by BMS. Thus, while Taxol may be more costly to produce than some cancer drugs, the prices announced by BMS bear little relationship to the manufacturing costs.

the cost of Taxol treatment

The total cost of a course of Taxol treatment will depend upon a number of factors, including the size of the patient, the type of cancer[5], and the response of the patient to therapy. A "cycle" of treatment is an injection administered every three weeks. Patients responding to therapy receive about eight cycles of treatment. The drug is sold in 30 mg vials. According to NCI officials, eight vials (240 mg) is a common dose for a single treatment cycle. For a patient using the eight vials per dose, Taxol will cost $1,169 per injection, and $9,350 for the full eight cycle course of treatment. BMS also offers discounts, including a sixteen percent reduction for certain government purchases.

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[3] While the FDA's action had been widely anticipated, the price of Bristol-Myers Squibb stock rose by 75 cents the day of the announcement, an increase in the company's market value of about $400 million (based upon 533 million shares). The increase in the stock price is reported in Timothy Noah and Elyse Tanouye, "FDA Approves Taxol to Treat Ovarian Cancer," *Wall Street Journal*, December 30, 1992.

[4] The $.60 mg that NCI had paid for the drug is thought to be higher than the current manufacturing cost, due to economies of scale from larger scale production.

[5] Under current NCI protocols, breast cancer patients receive about 30 percent more Taxol per treatment cycle than patients with ovarian cancer.

Table 1
NCI cost and Bristol-Myers Squibb price for Taxol
based upon eight 30 mg vials per treatment cycle

	milligram	*vial*	*8 vials*	*8 cycles*	*multiple*
NCI, before CRADA	.60	18.00	144	1,152	
Bristol-Myers Squibb					
wholesale	4.87	146.10	1,169	9,350	8.12
physicians direct	4.68	140.26	1,122	8,977	7.79
PHS	4.11	123.16	985	7,882	6.84

While there are many examples of drugs priced far above manufacturing costs, prices are usually defended on the grounds that the drug company has to recover large development costs, based on high risks. But in the case of Taxol, the role of the company was really minimal.

public and private investments in Taxol

In response to an inquiry from Representative Wyden, Dr. Samuel Broder, Director of NCI, said that prior to the Taxol CRADA, his Federal agency was "totally responsible" for the invention and development of Taxol, including:[6]

- initial collection and recollection of the bark,
- all biological screening in both cell cultures and animal tumor systems,
- chemical purification, isolation and identification,
- large scale production of material suitable for human use,
- development and production of suitable intravenous dosage formulation,
- preclinical toxicology,
- filing of an Investigative New Drug Application (INDA) with the FDA, along with all required documentation, and
- sponsorship of all clinical studies.

NCI says that it determined that Taxol would be an effective treatment for ovarian cancer in June 1988. In August 1989 NCI published a notice in the *Federal Register*, stating that it would chose a single firm to participate in a Cooperative Research and Development Agreement (CRADA) for the scientific and commercial marketing of Taxol. Firms were given just 45 days to respond, due to the "high priority" given to the development of Taxol. Of the four companies that responded, NCI selected Bristol-Myers Squibb (BMS).

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[6] Letter from Dr. Samuel Broder to Representative Ron Wyden, September 10, 1991.

Since the CRADA, BMS's primary contribution to the development of Taxol has been to supply NCI with Taxol for further clinical tests, and to pursue FDA marketing approval, which it received in December, in one of the quickest FDA actions in history.

BMS's costs of providing Taxol for the clinical trials was not trivial, but it hardly justifies the company's claims that it has spent huge sums on the development of the drug. The cost of providing 16 kilograms of Taxol for clinical trials would be less than $10 million, based upon NCI's costs of Taxol procurement before the CRADA was signed ($600,000 per kilogram). If BMS's was able to realize economies of scale in production, as NCI and BMS officials expected, then the cost would be even lower.

the Taxol CRADA

The nature of the Taxol agreements and the methods by which the government created the Taxol monopoly were complex and novel. Because research on Taxol, including its effectiveness in treating cancer, has been publicly reported in professional journals, neither the drug nor the idea of using it on cancer patients can be patented, not even by the Federal Government. Moreover, the only approved source for Taxol is presently the Pacific Yew, a rare and slowly maturing tree that is found mostly on Federal Lands.

In order to turn this very public discovery and resource into a private monopoly, the Federal government gave BMS the exclusive rights to harvest the Pacific Yew found on Federal lands[7], and it also gave BMS the exclusive rights to use federal research on Taxol.

The CRADA provisions giving BMS exclusive rights to use vast amounts of past and future government funded research were startlingly broad. They include historical research findings which were completed before BMS entered the Taxol picture, as well as "new studies and raw data" from future NCI funded Taxol research, which must be made "available exclusively to Bristol-Myers Squibb," so long as the company is "engaged in the commercial development and marketing of Taxol."

The data that BMS obtained the rights to includes the medical histories of sick persons who turned to government funded programs to receive experimental drugs. Information about whether these people live or die, or how they suffer, is now the exclusive commercial property of Bristol-Myers Squibb, under the CRADA.

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[7] Under the original agreement, BMS was given exclusive rights to harvest all Pacific Yew trees growing on lands managed by the Forest Service and the Bureau of Land Management, without any payment for the resource. After criticisms of the agreements were raised in Congress, the agreement with BLM was later modified to require token payments for the Yew tree bark.

The government's investment in Taxol research is extensive. In 1991 Dr. Broder estimated the taxpayers will spend about $35 million in past and future Taxol research,[8] including clinical trials on 30 types of cancer. Bristol-Myers Squibb is the only firm that will have access to the data from these trials.

When the agreement was signed it was anticipated that BMS would ask the FDA to designate Taxol as an Orphan Drug, for use in the treatment of ovarian cancer -- giving BMS a seven year monopoly on the marketing of Taxol. In the summer of 1992 BMS announced that it would give up its Orphan Drug protection for Taxol -- not because BMS wanted to allow new competition in the market for Taxol, but because NCI funded clinical trials indicated that Taxol is an effective treatment for breast cancer, a disease with a client population of 1.6 million, far in excess of the statutory limit for an Orphan Drug. But, while BMS will not obtain Orphan Drug protection, the company's exclusive rights to the Pacific Yew trees harvested on federal lands and the data from NCI funded Taxol research have created substantial entry barriers for firms that want to enter the Taxol market.[9]

In the future, BMS may face competition in the Taxol market. Recent research has indicated that new sources for Taxol may be available later. BMS has announced that it is investigating the production of Taxol from Yew trees growing in Asia and Europe, using technologies for which BMS now controls the patents. It is possible that other companies may develop their own technology for harvesting Taxol from these sources. The french company Rhone-Poulenc Rorer -- one of the unsuccessful bidders for the original Taxol CRADA -- is now attempting to win FDA marketing approval for taxotere, a Taxol analogue which it developed on its own. But in the near term, BMS will be the only source of Taxol for cancer patients, enjoying a marketing monopoly courtesy of NCI.

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[8] September 10, 1991 letter from Dr. Samuel Broder to Representative Ron Wyden.

[9] The agreement that gave BMS monopoly control over NIH research data, including data collected years before the CRADA was signed, was particularly innovative, and it has increased awareness of the importance of these type of records. At a recent conference sponsored by NIH and the Pharmaceutical Manufactures Association (PMA) on technology transfer policies, representatives from the drug industry spoke of the need to change state laws which give universities "ownership" over data and records from clinical trials. Officials at the National Institute of Allergy and Infectious Diseases (NIAID) recently entered into an agreement with Wyeth-Ayerst to give that company exclusive rights to use historical records from government funded research on Cold-Adapted Influenza Virus Vaccine, using the Taxol CRADA as a model.

What did the government get in return?

The federal government has received very little money from BMS. BMS will not pay the government any money for the exclusive right to use federal Taxol research. BMS will not pay the government any royalties for its sales of Taxol. BMS does pay royalties for the Pacific Yew tree bark collected from federal lands managed by BLM. At present those royalties amount to less than 1 cent per milligram of Taxol.

The government obtained BMS's promise to use its "best efforts" to commercialize Taxol, which was hardly a heroic gesture on BMS's part, given the high interest in this drug. BMS was also required to sign a "fair pricing" agreement.

Were the exclusive agreements necessary?

Taxol is expected to be a highly profitable drug with a very large market. There was never any finding that it was necessary to create a monopoly to ensure that the drug was developed commercially. Indeed, the investments by Rhone-Poulenc and other companies to develop Taxol analogues are convincing evidence that exclusivity wasn't necessary for the commercial development of Taxol.

NCI and Bristol-Myers Squibb assert that the exclusive contract was necessary to accelerate the development of Taxol. However, Bristol-Myers Squibb was shielded from the possibility that other companies would have obtained Taxol or used the Government's own clinical data on Taxol trials to file an earlier FDA application -- a particularly important issue when it was anticipated that Taxol would be protected under the Orphan Drug Act.[10]

According to some NCI officials, Bristol-Myers Squibb's main asset is its marketing expertise - it already sells more cancer drugs in the U.S. than any other firm. The BMS oncology empire is built on a number of other drugs that were invented through taxpayer funded research, including cisplatin, carboplatin, carmustine and lomustine, to mention a few. By giving Taxol to BMS, they argue, NCI was able to guarantee a smooth and efficient marketing effort. But to us, "marketing expertise" seems like a slender reed to justify this deal, since a promising new drug does not exactly require a hard sell, like a new brand of perfume.

---

[10] Think of the FDA approval process and the Orphan Drug Act as a race in which the firm that reaches the market first wins the prize. Did Bristol-Myers Squibb run faster because it had an advance guarantee that it would win? Or would cancer patients have been better off if the Government had allowed competition to determine who would bring the drug to market first?

The NIH fair pricing clause

The NIH "fair pricing" clause was developed reluctantly by NIH, in the wake of widespread criticism over the pricing of the AIDS drug AZT. NIH has used the "fair pricing" clause sparingly. According to NIH officials, the first two drugs to be priced under "fair pricing" agreements are ddi, an AIDS drug developed by NIH and licensed on an exclusive basis to BMS for 10 years, and Taxol.

At present there is little evidence that NIH will develop the mechanisms that are needed to make the clause an effective instrument to protect consumers and taxpayers. The standard NIH fair pricing clause states:

> 5.04 DHHS has responsibility for funding basic biomedical research, for funding medical treatment through programs such as Medicare and Medicaid, for providing direct medical care and, more generally, for protecting the health and safety of the public. Because of these responsibilities, and the public investment in the research that culminated in the Licensed Patent Rights, HHS may require LICENSEE to submit documentation in confidence showing a reasonable relationship between the pricing of a licensed product, the public investment in that product and the health and safety needs of the public. This paragraph shall not restrict the right of LICENSEE to price a Licensed Product or Licensed Process so as to obtain a reasonable profit for its sale or use. This Paragraph 5.04 does not permit PHS or any other government agency to set or dictate prices for Licensed Products or Licensed Processes. [emphasis added]

While the standard clause gives NIH the right to ask the company to submit documentation *in confidence* showing a reasonable relationship between the company's price and the public investment in that product and the health and safety needs of the public, the statement is deliberately ambiguous about what that relationship might be. Moreover, since the standard clause specifically rejects the government's authority to "set or dictate prices," it difficult to see what its purpose is, other than to give the government the right to ask for financial data, which cannot be disclosed to the public. A cynical interpretation would be that the clause is designed to benefit the company's political and public relations interests, by allowing it to claim that any price that satisfies the requirement is, by definition, a "fair price."

ddI

The first case where this clause was used was for the drug ddI. NCI officials told us that they were satisfied that the BMS price for this drug was "fair" because it was less than the price charged for the drug AZT. The irony of using a comparison to the price for AZT, which was widely considered to be excessive, is obvious. What NCI did not do is revealing. According to officials that we have interviewed, NCI never asked BMS to compare the price of the drug to the company's cost to manufacture, test and market ddI.

Taxol

The flaws in this approach are evident in the NCI's analysis of Taxol. The "fair pricing" clause in the Taxol CRADA was a decidedly abbreviated version of the standard clause. It reads:

> NCI has a concern that there be a reasonable relationship between the pricing of taxol, the public investment in taxol research and development, and the health and safety needs of the public. Bristol-Myers Squibb acknowledges that concern, and agrees that these factors will be taken into account in establishing a fair price for taxol.

Today NCI and BMS will argue that this clause does not permit NCI to require that BMS disclose its costs of developing and manufacturing taxol, even in confidence, and that BMS has declined to do so. In that case, how can NCI be expected to evaluate the company's self serving assertions?

But regardless of NCI's apparent reluctant to obtain any financial information from BMS, it is a matter of record that prior to its agreement with BMS, NCI was able to manufacture Taxol for about $.60 mg -- less than one-eighth the announced wholesale price. Moreover, by doing its own arithmetic NCI could easily determine that BMS's investments in the Taxol clinical trials were fairly modest.

How did NCI evaluate the Taxol price? Rather than focus on BMS's actual costs, NCI officials told the firm that it expected the drug to be priced in the range of other cancer drugs. NCI submitted to BMS a list of 15 drugs and their estimated "monthly wholesale cost."[11] BMS was asked to set the price so that a month of Taxol would cost no more than the median price for the group. NCI was, in essence, telling BMS that it could price Taxol, a government funded drug invention, the same as other cancer drugs were priced, regardless of where the funding came from, and regardless of how "fair" those prices were.

The median cost of the drugs on the list was $1,776. The highly arbitrary nature of the "list" is evident. There is one non-cancer drug on the list, human growth hormone (hGH) -- which is estimated to cost $2,520 per month. If a lower priced drug had been used instead, the median would have been the $1,030 for carboplatin -- priced 42 percent lower than the $1,776 median that obtains when hGH is included. Moreover, why did NCI choose the "monthly cost" when other comparisons, such as the cost of a completed treatment, are available? Why didn't NCI take into consideration such relevant factors as the size of the client population, or the types of intellectual property rights? Should Taxol be priced the same as drugs which benefit from exclusive marketing rights? There are few answers to these and other important questions.

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[11] The list included 13 cancer drugs approved by the FDA since 1988, plus cisplatin, a drug licensed by BMS from Michigan State University in 1978, and hGH, an expensive and controversial growth hormone drug.

Table 2
NCI's comparison drugs for purposes of pricing Taxol

drug	*"monthly" wholesale price*
gm-csf	4,095
c-csf	3,010
deoxycoformycin	2,880
hGH	2,520
mitoxantrone	2,010
ifosfamids	1,960
idarubicin	1,929
bcg	**1,776**
carboplatin	1,030
fludarabine	720
cisplatin	680
hexamethylmelamine	612
zoladex	322
flutamide	216
levamisole	100
Median price	1,776
Mean price	1,591

How did NCI's "list" compare to the actual prices set by BMS? The wholesale price for Taxol is $146.10 per 30 mg vial, or $4.87 mg. A patient who receive 8 vials per 21 day treatment cycle (a common dose), receives an average of 346.40 mg per month (based upon 4.33 weeks per month), for a cost of $1686.92, a few dollars less than the $1,776 median cost from NCI's list. Thus, while the NIH "fair pricing" clause eschews "dictating" prices, it seems that in the case of Taxol, NCI officials did indeed set the price. The problem, however, is that they set the price too high.

the NCI pricing model applied to levamisole

As a further illustration of the problems with NCI's approach, consider how this method would have worked if it had been applied to levamisole, the lowest priced drug on the list. Since levamisole is an important new cancer drug that can save the lives of many patients with colon cancer, it seems as though NCI would have determined that a far higher price, perhaps as much as $1,700 per month, was reasonable. But then consider other relevant information. Levamisole has been used for decades to deworm sheep at a cost of about 5 cents per pill. After NIH spent more than $11 million on levamisole research, leading to FDA marketing approval for the treatment of colon cancer, J&J set the price of the drug at $5 per bill, a one hundred fold increase over the price charged to farmers.

According to Dr. Charles Moertel from the Mayo Clinic, one of the principal investigators in the NIH funded levamisole research, J&J did little more than provide the government with the pills that were used in the studies, which, of course, were very inexpensive to manufacture.

I raised this issue with an NCI official who was involved in the Taxol negotiations, and I was told that the levamisole price was "no big deal," since it was such a "cheap" drug -- really a bargain by today's standards. Of course, had levamisole been priced for human consumption at the same it is still sold for use by sheep, the monthly cost of treatment would be about $1, roughly the cost of a bottle of aspirin. While some NCI officials think that consumers should be pleased to only pay $100 per month for the medication, many have been clearly outraged. And, since many cancer patients do not have the high incomes and good medical insurance that senior NIH officials have, this "bargain" looks like a rip-off.

Low-balling the Taxol price

One annoying feature of the discussion over Taxol prices has been the attempts by BMS and NCI to low-ball the actual cost Taxol treatment.

- BMS press releases claim that the average wholesale cost of a single treatment cycle of Taxol is $986.18. This is the cost of 202.5 mg of Taxol, or 6.75 30 mg vials. According to NCI's Drug Management Center, this is the amount of Taxol that would be given to a patient being treated for ovarian cancer, weighing about 105 pounds. A chart given to us by NCI says that patients actually receive between 7 and 11 vials, depending upon their size, and that 8 vials is a common dose. As noted above, the wholesale cost to a patient receiving 8 vials is $1,169.

- NCI officials have sometimes compared the cost of a single treatment cycle of Taxol to the "monthly" cost of other cancer drugs, but since Taxol is administered every three weeks, it is necessary to make a further adjustment.[12] The "monthly" cost of 8 vials of Taxol is $1,687 -- 58 percent higher than the $986 figure BMS uses to describe the Taxol price.

- While the FDA has only given Taxol marketing approval for ovarian cancer, the drug can and will be sold to treat breast cancer. Current NCI protocols call for 30 percent higher doses for breast cancer patients than for ovarian cancer. Since the client population for breast cancer is far greater than for ovarian cancer, it is fair to assume that the average cost of a treatment cycle will be significantly higher than BMS and NCI are telling the public.

- BMS says the average number of treatment cycles is four. Taxol patients receive one or two doses to determine if the patient is responding properly to treatment. If patients do respond to treatment, and the drug is not too toxic, they receive up to 8 treatment cycles, under current NCI protocols. Some patients may receive even more treatment cycles. By obfuscating the issue of the cost of a successful treatment, BMS and NCI have given cancer patients a misleading impression of the cost of Taxol. The wholesale cost of Taxol to a patient receiving 8 vial per cycle for 8 cycles is $9,350 -- far higher than the $4,000 "average" cost reported by the *New York Times*.

The efforts by BMS and NCI to put the Taxol price in the best light were politically motivated and misleading.

High prices as an R&D subsidy

Despite its modest role in the development of the drug, BMS has sought to give the impression that Taxol was an extraordinarily costly and risky venture. In a March 4, 1992 interview on the McNeil-Lehrer Newshour BMS spokesman Dr. Zola Horovitz said the company had made a "huge" investment, and that "Taxol will probably cost more than any other oncology product that's ever been developed." Other news reports have suggested BMS had spent $100 million on Taxol. According to BMS officials that we have talked with, however, most of the money that the company boasts of having spent on Taxol is money that has been budgeted for the development of new sources of Taxol or Taxol analogues. In terms of evaluating the risks to BMS, it is important to note that these investments come after NCI had completed Phase III trials, and after the NDA was already filed with the FDA, when the risks of failure were low.

The distinction between the company's costs of developing Taxol and the money it plans to spend to develop new sources of Taxol is subtle, but important. In the absence of the exclusive agreements with BMS, any number of companies could harvest the Pacific Yew tree and use NCI funded clinical trial data to obtain FDA marketing approval. This is a known technology that has already been developed through taxpayer funded research. If a company develops new methods of harvesting Taxol or if it can produce synthetic versions of the drug, these new technologies may be patentable. Indeed, BMS officials are actively licensing patents to do just that.

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[12] The 21 day dose is increased by a factor of 1.44..

Bristol-Myers Squibb wants to justify the profits it will earn on Taxol, the government funded invention produced from government owned trees, as necessary to fund this R&D effort. But to do so will make Taxol consumers a type of third class shareholders in BMS -- contributing capital but not receiving dividends. Consumers of Taxol should only pay for Bristol-Myers Squibb's costs of testing, manufacturing, and marketing Taxol. If the company wants to make investments in the development of new technologies, it should get the money from investors just as other drug companies do.

Suppose this argument is taken one step further. Does NCI believe that it could justify an even higher price for Taxol, if BMS promised to spend the money developing yet another drug, perhaps one to treat AIDS or heart disease? And if so, wouldn't this amount to a subsidy to BMS, forcing women with ovarian and breast cancer to pay for BMS's R&D efforts in new and possibly lucrative markets. What about companies that would be competing against BMS to develop those new drugs? Would the government then offer them similar bonanzas to finance their R&D programs?

Significance of Federally Funded Health Care R&D

The concerns about private sector prices for federally funded medical inventions are, of course, much broader than those raised by Taxol. Health care R&D is the second largest element of federally funded R&D -- only defense R&D ranks higher. The Bush Administration's fiscal year 1993 budget included more than $12 billion for health care R&D. About 70 percent of all federal health care R&D expenditures are funded through the National Institutes of Health. The remaining expenditures are funded through other agencies in the Department of Health and Human Services (HHS), as well as in the Departments of Defense, Energy, Veterans Affairs, the National Science Foundation (NSF), the National Aeronautics and Space Administration (NASA), and other federal agencies.

The federal share of all national health R&D expenditures is estimated to be about 42 percent, compared to 47 percent for private industry (the remaining 10 percent is funded by non-profit foundations and other sources). While the federal government plays a particularly important role in the funding of basic research, it also makes large investments in applied research, including many technologies that have enormous commercial value.

investments in clinical trials

Among the more interesting figures are the federal expenditures on human use clinical trials, a relatively advanced area for drug research. From fiscal year 1988 to 1993 NIH expenditures on clinical trials grew from $488 million to $869 million, an increase of 78 percent. By comparison, the members of the Pharmaceutical Manufactures Association (PMA) reported spending $1,333 on clinical trials in 1988 and $1,555 million in 1989 (the two most recent years for which data are available). For the years where we can make a comparisons, NIH is funding roughly one quarter of the combined costs of clinical trials.

Table 3
NIH and PMA Expenditures on Clinical Trials
(millions of dollars)

Year	*NIH*	*PMA*
1988	487.6	1,333.4
1989	495.5	1,555.0
1990	609.7	
1991	745.2	
1992e	843.8	
1993e	868.8	

Source: NIH Budget Formulation Office and PMA's *1989-1991 Annual Survey Report*.

Other federal agencies, ranging from ADAMHA to the Department of Defense also finance clinical trials of pharmaceutical products.

the timing of research investments

It is also important to recognize that the Federal Government tends to focus its research on more risky projects that occur earlier in the development stage than does the industry. This is important, because a dollar invested in an early stage of drug development is worth more than a dollar invested in a later stage. According to one study, the present value of a dollar invested in preclinical research is worth nearly twice as much as a dollar invested in Phase III trails, based upon the opportunity cost of capital alone (without making any adjustment for the higher risks of the preclinical research). Since the federal government tends to pay for the early costs of drug research, the relative importance of the Federal role in the funding of drug development is significantly understated by a simple comparison of government and industry year by year R&D expenditures.

Federal policies to transfer ownership of federally funded R&D

Policies concerning the allocation of intellectual property rights from federally funded research have changed markedly since the second world war. There once was a broad consensus that federally funded research should be liberally shared with the public, either by allowing research to enter the public domain, or by licensing property rights such as patents on a non-exclusive basis. In recent years this has given way to a more proprietary approach.

Many of the important changes in federal policy occurred in the 1980's. These include the enactment of the Stevenson-Wydler Technology Innovation Act and the Bayh-Dole University and Small Business Patent Procedures Act, both passed in 1980, the amendments to the Bayh-Dole Act passed in 1984, and the Federal Technology Transfer Act of 1986.[13] President Reagan also issued a number of Federal Executive Orders and memorandums which broadened the rights of government contractors and grant recipients to obtain titles to federally funded research products and grant exclusive licenses for commercial development.[14]

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[13] The Stevenson-Wydler Technology Innovation Act (PL. 96-480), Oct 25, 1980, encouraged the transfer of intellectual property rights from federal research to the private sector. It also provided for cooperative research agreements and for supporting Centers for Industrial Technology affiliated with non-profit institutions, which could take title to inventions developed with federal funds.

The Bayh-Dole Act University and Small Business Patent Act (PL 96-517), Dec 12, 1980, gave small businesses and non-profit institutions title to inventions that they developed under federal grants or contracts. The Act retained a license for government use.

A 1984 law (P.L. 98-620) repealed the 5-year limitation on the use of exclusive licenses by non-profit institutions that held title to inventions that had been developed with federal funds, and allowed non-profit organization to take title to inventions when operating government owned laboratory facilities.

The Federal Technology Transfer Act (PL-99-502), Oct 20, 1986, expanded the ability of agencies and laboratories to enter into Cooperative Research and Development Agreements (CRADAs). CRADAs typically involve joint research efforts between the government and industry, where a private firm obtains a promise that it will obtain exclusive commercial rights to research data and patents that are produced by the parties.

[14] February 18, 1983, President Reagan issued a memorandum instructing federal agencies, where not prohibited by law, to grant all contractors the same right to invention titles that the Bayh-Dole Act granted to small businesses and non-profit institutions. On April 10, 1987, President Reagan issued Executive Order 12591, instructing agencies to allow laboratories to enter into CRADAs and to develop a policy allowing contractors to retain rights to software and other technical data, with a reservation of royalty-free use to the government. The order also reaffirmed the policy in his 1983 memo of waiving government title rights to contractors wherever possible. On December 22, 1987, President Reagan issued Executive Order 13532,

These measures accomplished the following:

i. In those cases where federal research funds were managed by non-government personnel, contractors or grant recipients were given title to a wide variety of government funded research rights, with few restrictions on how these rights could be exploited.

ii. In those cases where the federal government retained title to the research products (such as research carried out by government employees or by contractors or grant recipients who were not qualified to take title to the research) federal agencies were told to place an increasing emphasis on exclusive marketing agreements with firms to commercialize the research products.

Patent, copyright, trade secret status and other measures are used to control access and ownership of government funded research. Private corporations routinely obtain exclusive marketing privileges on everything from government funded software and technical databases to inventions of new drugs.

The rationales for this more proprietary approach to federal research are varied, but two stand out, in terms of the frequency to which they are employed and the degree to which they are believed:

i. the need to provide incentives for the commercial development of a product, and

ii. the need to prevent foreign interests from benefiting from U.S. funded research and development.

While these rationales are contradictory (the need to prevent foreign companies from developing US technology suggests that sufficient incentives already exist for commercial development), they are often used simultaneously as a catch-all to justify policies.

These policy guidelines, which apply to all areas of federally funded research, have received wide bipartisan support in congress, due in no small part to aggressive lobbying and generous political contributions by companies in defense, energy, pharmaceutical, and other fields, which have benefitted from these transfers. Critics worry that universities are becoming too concerned with potential commercial rewards from research, and are abandoning important types of basic research or restricting the free flow of information among scientists. There are also concerns that the large emphasis on exclusive marketing agreements will harm consumers, or lead to anticompetitive practices, such as blocking the development of related technologies which would use the government research product as an input for a different

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requiring all agencies to remove licensing restrictions on inventions made with federal assistance.

product. Others have questioned the policies on the grounds that taxpayers should receive greater benefits from its investments. For example, in a minority report on the 1980 Bayh-Dole Act, which gave small businesses and non-profit institutions title to inventions developed under federal grants or contracts, Congressman Jack Brooks said:

> The major problem I have with H.R. 6933 is that it violates a basic provision of the unwritten contract between the citizens of this country and their government; namely, that what the government acquires through the expenditure of its citizen's taxes, the government owns. Assigning automatic patent rights and exclusive licenses to companies or organizations for inventions developed at government expense is a pure giveaway of rights that properly belong to the people.
>
> . . .The Federal government has the equivalent of a fiduciary responsibility to the taxpayers of the country. Property acquired with public funds should belong to the public. Deviations from that fundamental principle should be allowed only where a compelling justification can be shown and where the voice of the public can be heard in protest. This legislation stands that principle on its head by automatically conveying title or the exclusive right to use public property to private entities and placing the burden on the federal government to demonstrate that a retrieval of those rights is in the public interest.

Nowhere are these issues as important as in the medical field, where the public investment is enormous, and the product will not be a better microwave oven, but better health or even life itself. On the one hand it is important that there are proper incentives to develop new medicines and other health care technologies. On the other hand, consumers of medical technologies are uniquely vulnerable to monopoly pricing.

The Federal Orphan Drug Act is also an important mechanism for allowing private firms to obtain monopolies on government funded inventions. Since I have previously addressed this issue at length to this and other Committees of Congress, I will reference our earlier statements, and add only a few comments.[15] Today the Orphan Drug Act is primarily viewed as a mechanism to obtain seven years exclusive marketing rights (a feature that was considered unimportant when the legislation passed a decade ago). Thus, the Act is most important when company's do not hold patents for the drugs. A common reason that a drug cannot be patented is because researchers have already reported results in academic journals. This is more likely the result of research funded by the government than research funded by the industry, since the drug companies are known for exercising tight controls on a researcher's right to publish before applications for patents have been processed.

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[15] See James P. Love, "The Orphan Drug Act and Government Sponsored Monopolies for Marketing Pharmaceutical Drugs," comments submitted to the Senate Judiciary Committee's Subcommittee on Antitrust, Monopolies and Business Rights, January 21, 1992.

Because much government funded research ends up in the public domain (although less now than before), the Orphan Drug Act has become an important mechanism to obtain patent like protection on substances that cannot be patented, because of government funded research which has been published in academic journals.

limits on Administrative reforms

There are many things that the Federal government can do administratively to correct the woeful inadequacies of agency policies on the pricing of government funded pharmaceutical inventions. The federal government can develop better approaches to negotiating or setting prices on government funded medical inventions, it can collect better information on the economics of drug development and profits, and it can place more emphasis on competition, by requiring agencies to make findings that exclusive agreements are necessary, or by restructuring the negotiations for exclusive contracts so that companies negotiate on prices *before* partners are chosen for exclusive arrangements (getting more mileage from the *ex ante* competition that exists in these awards).

But there are also many problems that cannot be solved without addressing the reforms in the Bayh-Dole University and Small Business Patent Procedures Act or the Orphan Drug Act -- two deeply flawed laws that have very powerful constituencies. So long as the federal government grants titles to federally funded research conducted by Universities and other contract and grant recipients, the Congress will not be able to control prices for many government funded drugs. For example, the 1990 NIH health care R&D budget included $4.18 billion in work performed by universities and another $1.8 billion was performed by other non-profit institutions.[16] Until the Bayh-Dole Act is changed, the Federal government will be severely restricted in its ability to control prices for many important drugs inventions that taxpayers have financed.

The cost of new pharmaceutical inventions

Most recent studies of the costs of developing new drugs have focused on the "green field" cost of drug development. That is, the studies look at the industry' cost of drug development, when the company finances all development, including investments in pre-clinical research. Because there is little data in the public domain on the economics of drug development, the best known research has been carried out by economists who work closely with drug companies, relying upon their consulting relationships to gain access to confidential data. The study which has received the widest exposure on Capital Hill is a 1991 paper by Joseph DiMasi, Ronald Hansen, Henry Grabowski and Louis Lasagna, researchers from Tufts University,the University of Rochester and Duke University.[17] I will refer to this as the DHGL study.

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[16] This included about $2.5 billion in funding of basic research at universities and colleges, which was nearly half of all federal funds for basic research given to colleges and universities. U.S. Department of Health and Human Services, *NIH Data Book, 1991*, NIH Publication No. 91-1261, (Bethesda, MD: NIH, September 1991).

DHGL's analysis has its strengths and weaknesses. The strength of the analysis is the availability of project level information from 99 "new chemical entities" (NCE), provided by 12 U.S. owned pharmaceutical companies. The weakness of the study is the lack of data on pre-clinical investments, which were estimated from aggregate data using assumptions that may or may not be accurate. The bottom line of the DHGL study is that the cost of developing a NCE is estimated to be $231 million. This figure, which is widely quoted, includes both cash outlays, adjusted for inflation, and imputed costs. The imputed costs include an adjustment for the "dry hole" risk of investments, and also the company's opportunity cost of capital, assumed to be a real rate of 9 percent. For example, if a company invests a dollar at a point where the chance of success is only 25 percent, it is counted as four dollars, and then increased again to reflect the opportunity cost of money. In their report, the average cash outlay of $2.134 million for Phase I trials is adjusted for both risk and opportunity costs, and counts as $17.8 million.

We are currently undertaking an analysis of the DHGL study, as well as other estimates of the costs of development for new drugs, and we are not prepared at this time to provide the Subcommittee with our findings. But there are several factors which the Subcommittee should keep in mind.

1. First of all, the DHGL estimate of $231 million was far higher than previous estimates. For example, a 1987 study authored by Wiggins for the PMA, estimated the cost to be $125 million, and a 1979 study by Hansen estimated the cost to be $54 million (in 1976 dollars). Earlier studies, many of which were flawed on methodological grounds, came up with figures from $.5 million to $21.8 million.

   The fact that the DHGL study was considerably higher than previous estimates isn't itself a criticism of their finding. It is conceivable, for example, the costs of developing new drugs is itself increasing, as evidenced by the rapid escalation in the prices of new drugs, as well as the new incentives to invest that those high prices create. If so, then Congress should redouble its efforts to control drug prices, particularly when the company does not bear the full costs and risks of development, since the stakes are increasing.

2. Next, the Subcommittee may be interested to know that more than half of the $231 million estimated by DHGL was assigned to the opportunity cost of capital. That is,

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[17] DiMasi, Hansen, Grabowski and Lasagna, "Cost of innovation in the pharmaceutical industry," *Journal of Health Economics*, 10, 1991, pages 107-142.

DHGL estimate that the cash outlays, adjusted for risk, are $114 million, and the rest represents the profits that the company needs to satisfy investors. Thus, if a company were to receive $231 million in profits from drug sales in its first year, it would have "broken even" on the drug, including the necessary shareholder returns.

3. Third, the Subcommittee will probably be surprised to learn that DHGL assume that two thirds of all costs are related to the pre-clinical stages of development. This figure is really the softest part of their analysis, but it does suggest that the cost of developing drugs that have already entered the clinical testing phase is quite low. As a related issue, by the time a drug enters Phase III trials, DHGL conclude that more than 85 percent of the cost of the drug has already been paid for. The Committee should keep this in mind when looking at the prices charged for ddI and Taxol, where BMS entered the picture quite late.

The development of better models for pricing government funded pharmaceutical inventions.

The pricing of pharmaceutical drugs is an important task that deserves a higher level of attention than it has received to date. Federal policy makers, academic researchers, and citizens need better economic data about the costs of drug development, manufacturing, and marketing, and also about drug revenues, both in the U.S. and in the world market, where drugs are sold. The fact that Bristol-Myers Squibb can simply refuse to provide details on its investments in Taxol is a shocking example of the current state of ignorance about drug prices.

Congress and the Administration should undertake a broad inquiry into the types of data that researchers and policy analysts believe are necessary to shed light on a wide range of drug pricing issues, and then create programs, backed by new disclosure laws, the broaden the public's knowledge of this important public health issue. Health care research is more than a search for new chemical compounds. It is a search for economically feasible ways to improve national health care.

Second, federal agencies should not assume that exclusive license agreements and CRADA's are always necessary. Agencies who pay for the development of pharmaceutical research should be required to make findings that exclusive agreements are in the public interest. These findings should include an economic analysis of the markets for the inventions. The fact that NIH never made a finding that an exclusive agreement was necessary for the development of Taxol is a grave mistake, given the prices that consumers will have to pay for the BMS monopoly.

Third, NIH and other federal agencies managing federally funded health care R&D need to begin anew to develop workable models to introduce price competition into CRADA and license negotiations, so that the *ex ante* competition that exists before exclusive agreements are issued can be used to determine prices.

Fourth, Congress and the Administration need to develop models which can be used to determine reasonable prices under a wide range of mixed funding scenarios, including cases where government funded research creates windfalls for companies that obtain monopoly marketing protections under the Federal Orphan Drug Act, or where the government's research creates new markets for drugs that are patented by private firms. For example, when a private company such as MicroGeneSys can hire a former United States Senator to lobby Congress to put a $20 million appropriation into the Defense Department's budget to carry out clinical trials one of its drugs, the taxpayers have a right to ask how the public will benefit from this investment.[18]

We are currently working on the development of models that can be used by the federal government to:

a) determine if an exclusive agreement is in the public interest,

b) increase price competition in negotiations on exclusive agreements, and

c) determine reasonable prices for drugs developed with mixed funding.

We are working with Professor David Genesove, a member of the economics faculty at the Massachusetts Institute of Technology, and other experts. We anticipate the competition of preliminary findings in March, and will be happy to share them with members of this Subcommittee.

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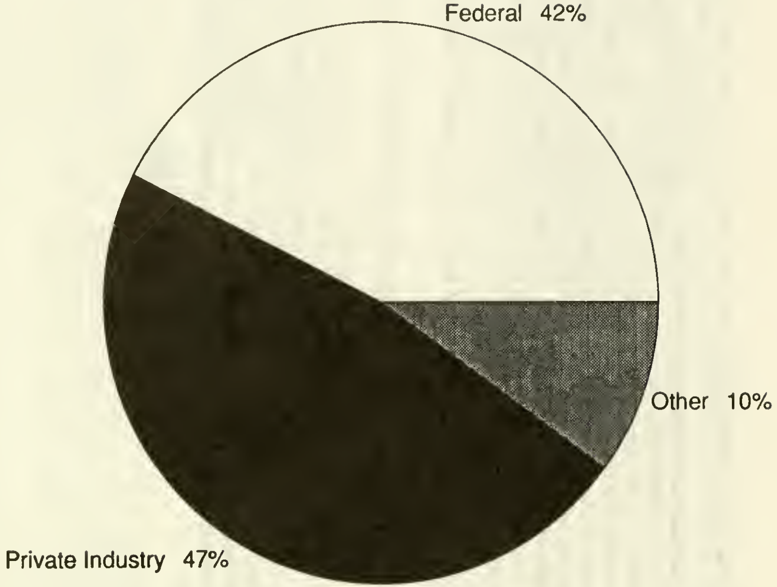
[18] William Hines, "How MicroGeneSys sought the inside tract on an AIDS drug," *the Progressive*, February 1993, page 29-31.

Figure 1

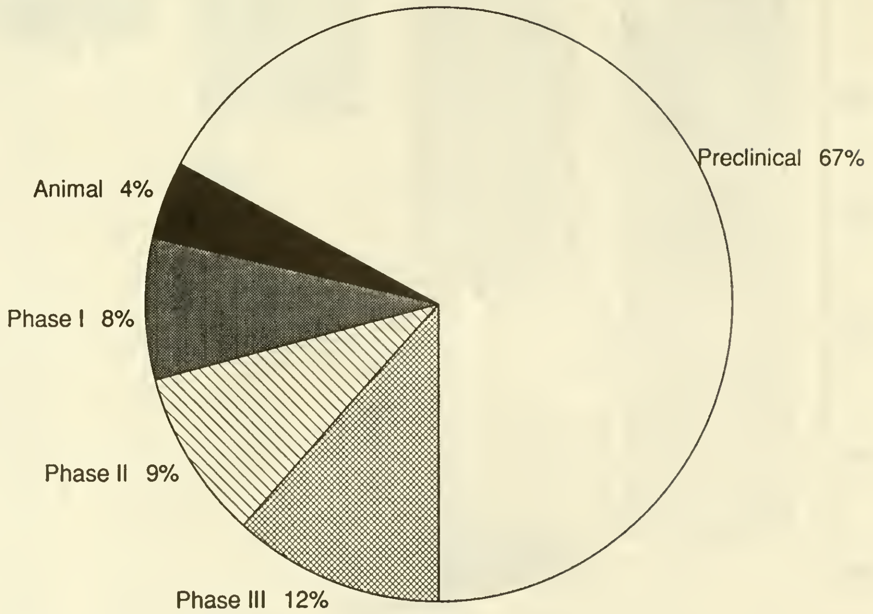
Sources of Funding for U.S. Health Care R&D
(1990)



Source: National Institutes of Health

Figure 2

Estimated Shares of Drug R&D Costs

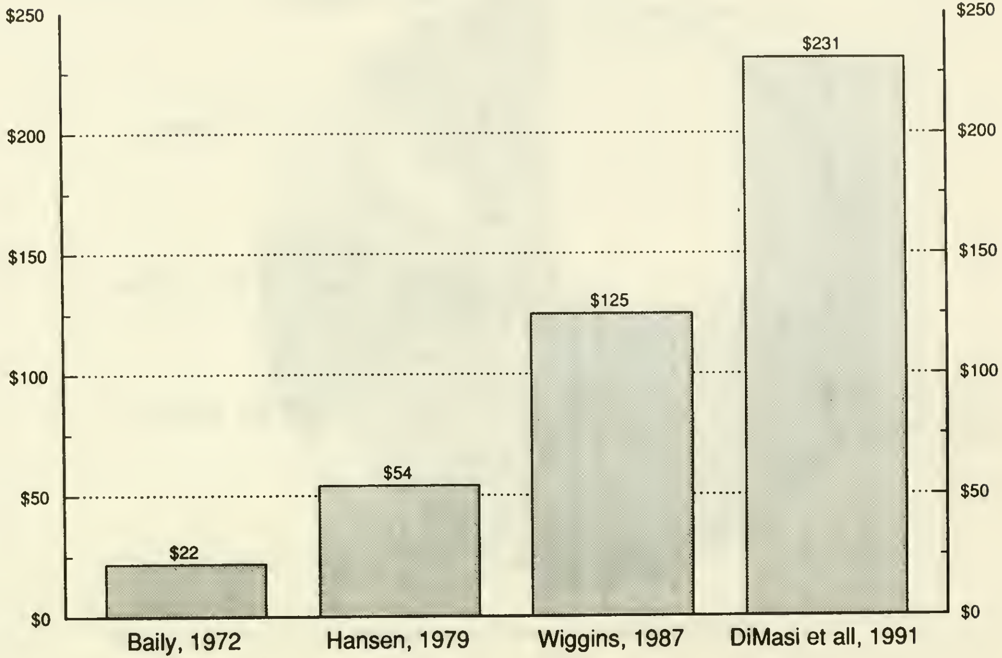


Source, DiMasi, Hansen, Grabowski and Lasagna 91

Figure 3

Studies of Drug Development Costs

(millions of dollars)



TESTIMONY OF KAREN GUTH

Testimony before the U.S. Congress Small Business Subcommittee.
January 25, 1993

Good morning Congressman Wyden and other distinguished members of this committee. My name is Karen Guth, I live in Denver Colorado with my husband and our two beautiful sons. I graduated from the Colorado College with honors, I went on to complete my Masters of Arts in teaching, I teach and I work in a myriad of volunteer positions in my community. I will be 35 years old in March and I have a rare genetic disorder called Gauchers disease which affects approximately 22,000 Americans- the majority of whom are of Eastern European Jewish descent. My physical handicaps have generated obstacles for me; however, thanks to the strong and constant support of my family, I have been able to become a productive and caring member of our society.

Today I am here to tell you about my battle against the drug company, Genzyme Corp. This is a company which used the NIH research results, funded for over 35 years by our tax dollars and private donations, to create a multi-million dollar corporation at the expense of the health insurance companies, the government sponsored medicaid program and worst of all at the expense of the emotional and financial well-being of the people who are afflicted with a debilitating disease.

The Genzyme Corporation has taken the Orphan Drug Act, intended to help people in my situation, and they have interpreted it to the full extent of their greed. As you know, more and more companies will follow in their barbarous footsteps if we do not stop them now. Our government gave the NIH money to discover these treatments and now the government is forced to pay for the drugs when the patient's health insurance runs out. Because of the gross costs of these drugs, the patients must then resort to accepting Medicaid in order to continue to obtain these life-saving medications.

The Genzyme Corporation is currently the only company manufacturing a drug which could treat my physical disease and enable me to have more energy for the activities to which I am committed. However, they are asking nothing less than for me to exchange my mental, emotional, and financial well being for my physical health. For me to take ceredase, the treatment developed by Dr. Roscoe Brady at the NIH, it would cost $350,000 a year. This is just the cost of the drug! We have a family health insurance policy that has a lifetime cap, and once we have met that limit my family would be left without health insurance.

The Genzyme Corporation, Vice President, Mr.William Pursley and a slew of their reimbursement specialists have called me during the past few years to implore me to take their drug, with the assurance that Genzyme's attorneys would force my health insurance company to reimburse them. Genzyme Corporation is spending a fortune marketing their product, Ceredase, through magazine publications, video productions, conferences, and lavish, all expense paid seminars, for medical professionals.

Now you may ask, as I have, why would a drug company so aggressively market directly to patients? They do this because they know that, once a person who has lived with a debilitating chronic illness starts to feel better, through dependency upon Ceredase, we will sacrifice anything and everything to continue to get our treatment. Like a "junkie", we will use up our health insurance, we will quit our jobs, we will divorce our spouses so that we may declare ourselves legally indigent to receive Medicaid. All the while Genzyme Corporation is collecting unprecedented revenues (they are now the third most profitable drug company in the US and they are only treating approximately 500 Gauchers patients world wide).

My recommendations to this committee are as follows:

1) I implore you to investigate the Genzyme Corporation, and the NIH. Learn the truth about how the drug, Ceredase, was developed over the last 35 years with tax dollars and private donations, by the NIH, not the Genzyme Corporation. Find out how the price of Ceredase was established, and why after the NIH developed it, Genzyme has all rights and privileges to charge abhorrent prices for it? Demand that Genzyme corporation make a full disclosure of its costs for, both the original Ceredase, derived from human tissue, and the new "biotech" or recombinant product. Discover who from the NIH "sold -out" to the Genzyme corporation and what other government paid researchers are "selling-out" to other "Johnny come lately" drug companies for a piece of these enormous "nitch-market" profits?

2) Set a cap on the amount of profit a drug company can make on a medication under the orphan drug act. After that cap is reached allow competition to ensue in order to moderate the price and allow people to continue to receive the drug without the fear of exhausting all of their health insurance funds.

3) Set a fair price for an orphan drug from its onset into the marketplace. This should ensure that the drug company not only recovers its cost and that it makes a fair and reasonable profit, but it will ensure that there will not be a demand for further government funding for patients (i.e. Medicaid) to continue their treatment.

The Genzyme corporation and their cohorts at the NIH have perpetrated the worst kind of crime against humanity, one that robs people of their dignity, one that robs people of their ability to be free, independent and productive members of a society. A crime which in the end will rob us all of a piece of our humanity. I do not want them do this to me. Today I am here to ask you to help me speak up for the victims of their avarice, because in the end their greed will not be satiated after it destroys me, then they will come after you and your families and utterly destroy us all.

Thank you.
Karen Guth
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National Organization for Rare Disorders, Inc.
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out of the darkness
into the light

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THE FEDERAL ROLE IN COMMERCIALIZING MEDICAL RESEARCH: SHOULD SOCIETY GET A PAYBACK?

TESTIMONY OF

ABBEY S. MEYERS

EXECUTIVE DIRECTOR

NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD)

TO

HOUSE OF REPRESENTATIVES

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES & ENERGY

HONORABLE RON WYDEN, CHAIRMAN

JANUARY 25, 1993

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* Associations are joining continuously. For newest listing please contact the NORD office

Dedicated to Helping People with Orphan Diseases

11/92

Mr. Chairman, and members of the subcommittee, I am Abbey Meyers, Executive Director of the National Organization for Rare Disorders (NORD). Our organization is a non-profit voluntary health agency and a coalition of 127 national voluntary health agencies and support groups dedicated to rare "orphan diseases." Under the Orphan Drug Act of 1983, an orphan disease is an illness or condition that affects fewer than 200,000 Americans. There are more than 5,000 of these disorders that combined together affect approximately twenty million Americans.

NORD was initially formed to assure that orphan drugs - drugs that have little commercial value - would be developed and manufactured for the limited populations of patients who desperately need them. The decade since the Orphan Drug Act was enacted marks many remarkable accomplishments of a unique government/industry partnership that has alleviated substantial pain and prevented thousands of deaths. But it is also symbolic of many factors that have led to the health care crisis which exists in America today. It has taught us the important lesson that the government can initiate the most well intentioned programs to benefit the downtrodden and medically disenfranchised populations who we all care about, but without very tight controls and oversight, someone will take advantage of that program and abuse it. Mr. Chairman, "deregulation" and abdication of regulation in the health care sectors has been a disaster.

The fact is, during the early 1980's Congress launched several ingenious initiatives to transfer technologies out of government laboratories and put them in the hands of private enterprise. Even decades before that there was a recognition by many government scientists and administrators that the therapies discovered in their laboratories were not being adopted by the pharmaceutical industry, and clearly patients could not benefit from products in the absence of commercialization. These therapies included not only orphan drugs (drugs of little commercial value), but other drugs for very large populations of patients.

The National Cancer Institute was probably the first to initiate a drug development program for cancer therapies. NCI screened compounds for activity against cancer, then supported related clinical trials. After the success of the NCI program became apparent, other Institutes began programs to develop drugs for other conditions.

These targeted pharmaceutical development programs are run by NIH and they chemically synthesize new compounds, screen potential compounds for pharmacological activity, conduct preclinical toxicology and pharmacology studies, and conduct or support clinical trials and production of the compound. Some of these programs are:

National Cancer Institute:

Developmental Therapeutics Program
Cancer Therapy Evaluation Program
Biological Response Modifiers Program

National Heart, Lung and Blood Institute:

National Sickle Cell Disease Program
Lung Surfactant Replacement Program

National Institute of Allergy and Infectious Diseases:

AIDS Program
Antimicrobial Chemistry Program
Antiviral Research Programs (Non-AIDS)

National Institute of Neurological Disorders and Stroke:

Anticonvulsant Drug Development Program (For Epilepsy)

National Institute of Child Health and Human Development:

Contraceptive Development Program

Other government agencies develop vaccines, diagnostics, medical devices and various other medical products.

Some of the drugs that emerge from these programs are supported through CRADAs, SBIR grants, or other formal and informal mechanisms. The government, however, has no mechanism to assure that the prices of these products reflect the degree to which the taxpayer has subsidized the research and development (R&D) of each product.

Moreover, there are many other government agencies that participate in development of medical products including the Dept. of Defense (DOD), Dept. of Education, Food & Drug Administration (FDA), Veterans Administration (VA), Dept. of Energy (DOE), Centers for Disease Control (CDC), National Institute of Drug Abuse (NIDA) and the Alcohol, Drug Abuse, Mental Health Administration (ADAMHA). Some of these agencies have in-house programs, but most support development of products through research grants and contracts, including CRADAs.

In 1980 Congress passed the Stevenson-Wydler Technology Innovation Act, which initiated the current era of government sponsored commercialization. The Small Business Innovation Development Act (PL97-219) was passed in 1982, which marked an important federal effort to assist private enterprise. Concurrently, this was the beginning of the period of unprecedented drug price inflation, with most pharmaceutical companies blaming their extraordinary price hikes primarily on the increasing costs of R&D even though the government was playing an increasing role in subsidization and drug company profits grew at an annual rate of over 10%!

PL97-219 provided Small Business Innovative Research (SBIR) grants to small companies willing to commercialize drugs that were discovered and often tested with government funds. Federal agencies with an annual extramural research budget of more than $100 million are still required to reserve around 5% of their budget for the SBIR program. In most cases, the government agency identifies the kind of research they want the company to do. This means that the government in a sense contracts with a company to bring a product to market, with no strings attached.

That is, the company doesn't have to pay the development money back to the government, and it enters into no agreement with the government as to the price it will charge for the product once it is commercialized.

In 1986 the Federal Technology Transfer Act amended the Stevenson-Wydler Technology Innovation Act of 1980, and that created CRADAs. As you know, CRADAs did not initially require that emerging products be sold to the public at a "reasonable price," and the real problems became apparent when AIDS therapies, subsidized by the government, reached the retail market.

Speaking as an ordinary health care consumer and taxpayer, most Americans are outraged at the prices being charged for new prescription drugs, but when R&D is federally subsidized we particularly resent that we must pay for them many times over: We pay for them through our taxes when they are being developed with government funds; we pay for them when we buy them; we pay for them through the inflated costs of our health insurance premiums; and we pay for them again through Medicare and Medicaid taxes when the government has to purchase them for the elderly, disabled or poor.

It seems that everybody is making a buck out of these drugs except for the patients and taxpayers who are devastated by their costs. Even when Congress became outraged at the prices being charged for many pharmaceuticals, you put your foot down and demanded mandatory discounts for Medicaid, but not for ordinary consumers. The burden of illness is unbearable in America. Added to the physical pain and mental anguish associated with any serious or chronic disease is the fact that we get ripped off every time we walk into a local pharmacy, and again when we pay our taxes.

The pharmaceutical industry says its inflationary pricing is necessary because of the escalating costs of research and development and the high risks of R&D. But developing a drug under a CRADA or an SBIR grant means there is usually little risk involved. Only when the government already knows that a drug is of significant importance does it seek a sponsor to commercialize it, so there is diminished risk that the drug won't actually get to the market. Many drugs developed under CRADAs are significant breakthrough drugs.

The R&D "risk" the drug industry is concerned about is the risk associated with developing "me too" drugs that are usually developed in their own laboratories in an endless quest to win a piece of a very lucrative market from another company. First, they have no guarantee that the compound will prove safe and effective through many years of expensive testing, but secondly, if they can't prove that their drug is in some way superior to similar drugs, they may experience marketing difficulties. The innovator company usually has a substantial advantage and maintains the majority of the market unless a newer drug can prove clinical superiority. How much of the industry's R&D expenditures are going toward true breakthrough treatments, and how much of it is going to "me too" drugs that represent only slight variations of marketed drugs that won't infringe upon a competitor's patent?

Moreover, drug companies tend to specialize in certain types of drugs. For example, Bristol-Myers Squibb Company is the recognized leader in cancer drugs. This probably happens because the research divisions of large drug companies tend to hire staff who specialize in certain scientific areas. They often hire these scientists from NIH where the pay scale is quite low. Eventually the company's marketing staff builds up a relationship with specialist physicians (e.g., oncologists). It would therefore be very difficult for other companies to compete with Bristol-Myers Squibb's cancer drugs because it would be very hard to attract the types of scientists who develop oncology drugs, and their marketing staff might not have equivalent access to practicing oncologists. Similarly, companies might have difficulty developing and marketing a cholesterol lowering drug because they would have to compete with Merck, the recognized leader in the field.

When we look at some of the drugs that have been subsidized or substantially developed with government funds, and the prices that some companies are charging for these drugs, we can only ask why it has taken so long for Congress to look at the problem, especially after the AIDS epidemic brought this issue to the forefront. Some of those drugs are:

Drugs	Disease
Human Growth Hormone	Pituitary Dwarfism
Erythropietin	Anemia
Lung Surfactant	Respiratory Distress Syndrome
Rimantadine	Influenza A
Carbamazepine	Epilepsy
Clonazepam	Epilepsy
Sodium Valproate	Epilepsy
Clorazepate	Epilepsy
Alglucerase	Gaucher's Disease
Hydroxyurea	Sickle Cell Disease
Cetiedil Naltrexone	Heroine Addiction
Most Cancer drugs	
including: Taxol	
Cisplatin & Levamisole	Cancer
Acyclovir	Herpes Virus
Most Aids drugs including:	
AZT	AIDS
DDI	AIDS
DDC	AIDS
Ganciclovir	AIDS Infection
Ribivarin	AIDS Infection
Pentamidine	AIDS Infection

Some of the prices of these drugs include $30,000 per year for human growth hormone, $6,000 per year for EPO, $380,000 per year for Alglucerase (Ceredase), and $3,000 or more per year for AZT. When AZT was initially approved for marketing, it cost approximately $8,000 to $10,000 per year, per patient. Burroughs Wellcome, however, was one of the few companies to lower their price on a marketed drug and concurrently the average dosage of AZT was reduced. Nevertheless, EPO, AZT and human growth hormone are designated orphan drugs that all appear on the list of the world's fifty top-selling drugs. Orphan drugs, you will remember, are supposed to have little commercial value!

Even today, some post marketing studies on lucrative FDA approved drugs are supported by NIH, no matter how profitable the drugs are. Right now, for example, studies are being conducted with human growth hormone on short children who are perfectly healthy, and Proscar for prostate disease. These may be significant studies, but who do they really benefit - the patients or the companies? Why isn't the FDA or NIH empowered to require drug companies to finance these post-marketing studies if the protocols are so important?

Not all of the drugs listed above were developed with CRADAs, because CRADAs are just a recent legitimization of informal and formal policies carried out by the government's research institutions for many years. For some of these drugs, most of the ***basic research*** was carried out at NIH and companies capitalized, as they should, on government discoveries; some of the drugs were discovered in private laboratories and the government conducted or paid for the clinical trials; some drugs were discovered and/or developed through government grantees; and some benefited from intramural research projects, etc. ***Just about every cancer and AIDS drug has received government support at some point in its development***, but only a very small number have had an obligation to be "reasonably priced."

I want to clearly state that this research is a wonderful thing for the government to do, and we would not want to change the system. Many of these important drugs would not have been made available to American patients without the government's support and its aggressive enticement of commercial sponsors. If anything, these programs should be expanded, not diminished. But the prices society pays for the finished products must be regulated by the government. Let me give you a few examples:

> Levamisole is a drug that is commonly given to sheep to prevent worms. It costs farmers six cents per pill. However, the National Cancer Institute (NCI) believed that this drug could be used in humans for treatment of colon cancer. For twenty years NCI supported the research on Levamisole's use in humans, and found that it could prevent 7,000 deaths each year. In 1990 FDA approved the drug for colon cancer. The only difference between the veterinary product and the human pill is its size (the pill for humans is smaller). When you buy the pill from a veterinarian it costs six cents each, but when you buy it in your local pharmacy it costs more than $6.00 each.
>
> When the primary biomedical researcher (Dr. Charles Mortell), who conducted the clinical trials under NCI grants, asked the manufacturer why they had increased the price so much for the human drug, the company told him that increased ***marketing costs*** was the primary reason (ABC's Prime Time Live, June 19, 1992). The manufacturer, according to the researcher, paid nothing for the clinical trials.

Probably the worst example of government indifference and corporate greed is Ceredase, a drug developed substantially with federal funds for the treatment of Gaucher's disease. Make no mistake about it, Gaucher's is a horrible life-threatening disease. It causes liver, spleen and bone damage, and ultimately the bones completely dissolve. There is absolutely no doubt that Ceredase is a miracle drug.

The OTA report, "Federal and Private Roles in the Development and Provision of Alglucerase Therapy for Gaucher Disease" (OTA, 1992), says that although the manufacturer claims it spent $48.6 million developing Ceredase, it actually cost them only $29.4 million. The company sold over $80 million worth of Ceredase in its first year on the market. This drug costs the average adult Gaucher's patient $380,000 per year, and they must take the drug every year for the rest of their lives. But NIH scientists discovered this drug and the government spent millions of dollars developing it, including grants and contracts to the manufacturer.

Another example is the drug erythropoietin (EPO). In the early 1970's researchers at the National Heart, Blood and Lung Institute (NHBLI) discovered EPO. They mounted a campaign to purify EPO so it could be given in therapeutic doses to people with serious anemia. They issued a Request for Applications (RFA) in 1976 to purify EPO, but since it could be collected only in very tiny amounts from urine it proved very difficult to collect enough of it to mount substantive clinical trials.

Meanwhile, the federal government encouraged and supported development of the infant biotechnology industry. Indeed, the U.S. biotechnology industry is the result of 40 years of federally funded research, mostly to academic scientists. It was through government sponsored research that science learned how to clone and express genes so they could make large quantities of natural human proteins (Biotechnology - the Enormous Cost of Success, R. Doolittle, NEJM, May 9, 1991, pgs. 1360-61). Biotechnology companies benefited from these discoveries, and finally recombinant erythropoietin was commercialized at the end of the decade.

Several biotechnology companies saw an opportunity with EPO, and they took it. Since the government did not give them money, they owed nothing to the government. However, the company that reached the market first obtained an orphan drug designation for EPO, even though it was never intended to be a "drug of little commercial value." By getting the drug approved for the type of anemia that is associated with renal failure instead of anemia in general, the population of patients falls under 200,000 Americans. But the manufacturer charges about $6,000 per year, per patient, and Medicare is the primary payer since end stage renal disease (ESRD) patients automatically qualify for Medicare.

> Under the Orphan Drug Act the manufacturer gets seven years exclusivity, thereby blocking all competitors from the market, and they get tax credits to subsidize the costs of their clinical research. EPO sold more than $300 million in 1991. This led to the HHS Inspector General calling for substantial revisions of the Orphan Drug Act. (The Effect of the Interim Payment Rate for the Drug Epogen on Medicare Expenditures & Dialysis Facility Operations, May 1990, Richard P. Kusserow and Curing the Orphan Drug Act, J. G. Thoene, Science, Vol. 251, pgs. 1158-1159, 1991).

In the words of Dr. R. Doolittle, "Naturally, those who invest in the development, manufacture, and distribution of these (biotechnology) products are entitled to fair and reasonable profit. But the public also deserves that these drugs, the products of long-standing public investment, be made widely available at fair and reasonable prices" (NEJM, May 9, 1991). There is no requirement, outside of CRADAs, to charge "reasonable prices" for any pharmaceutical, and the absence of a definition for "reasonable price" makes the CRADA requirement unenforceable.

Why is there so much discrepancy between the amounts manufacturers claim they spend on R&D, and the smaller amounts claimed by outside experts? In the case of Ceredase, OTA included only the actual expenditures for work, materials and facilities needed for R&D. Companies often add marketing research, lost opportunity for investment income, and many other elements.

An increasingly popular methodology being employed by drug companies is called the "Research Partnership." Instead of the company spending its own money to develop a drug, it starts a separate corporation for the purpose of "off-balance-sheet financing." Investors who buy shares in the research partnership are told it is an "R&D Spin-Off", and if they invest they are certain to receive a hefty profit. Around the time that the drug gets approved, the parent corporation buys back the shares of the partnership at a very large profit. The money they spend to buy back those shares is categorized as a "research expense" which they can deduct from taxes. Therefore, if they borrowed $20 million from the partnership to develop a drug, and if they buy those shares back at $40 million, the research expense on their ledgers is $40 million, not $20 million.

How can these problems be corrected while not discouraging technology transfer from government research institutions to the private sector? We patients, and academic scientists, are dependent upon the pharmaceutical industry to bring our drugs to market. These companies must make a profit. The challenge is to define what is "reasonable" and what is "excessive." The government visionaries who developed these programs served society very well, and in the future arrangements such as CRADAs and SBIR grants will only grow in importance because drug companies must be enticed into certain medical areas.

In the meantime, there are areas of drug R&D that are still being neglected. For example, our nation's "war on drugs" is a farce. We can't win this war unless we reduce demand for recreational drugs, and we can't reduce the addict's craving without treatment. Yet pharmaceutical manufacturers do not want to get involved in development of these treatments, primarily because Medicaid would be the primary payer. So the only way treatments for addictions will get developed is through government assistance, and at times, aggressive arm twisting.

The fact is, the rest of the industrialized world regulates pharmaceutical prices the way we regulate utilities, and since just about all U.S. and multi-national companies sell their drugs in Europe, it is highly doubtful that they will decide to pack up their marbles and go home if we don't play by their rules in the U.S. We are the last free market in the world for pharmaceuticals, so there is no place for them to go where they can escape price regulation. Moreover, the industry must recognize that with government privileges, such as CRADAs, should come responsibilities to the public which has granted those privileges.

But NIH should not be making pricing decisions. Let NIH handle the medical issues, and the accountants should handle the financial issues. Moreover, it would be a conflict of interest for NIH to participate in pricing decisions since NIH scientists, and NIH laboratories, get royalties from CRADA products. So it is to NIH's benefit to approve high prices for CRADA drugs.

Pricing could be determined by HCFA, the GAO, OMB, the HHS Inspector General, or any one of dozens of other federal agencies who are expert in finances. However, any department assigned with the task of pricing drugs that are developed with government funds, should also have medical people, patient representatives and policy leaders who can consider other factors such as a drug's contribution to society.

For example, in some countries, new drugs are not approved for reimbursement unless the manufacturer can show that the drug is safer or more effective than currently marketed products. Pricing decisions are often based on whether the product is a "me-too" drug, or a minor or major therapeutic advancement. In our country perhaps a formula should be developed for CRADA drugs so that manufacturers will be able to estimate in advance what their costs and profits will be. For example, the cost of R & D, plus manufacturing costs, plus pre-set indirect costs and a profit percentage, plus a bonus of specified profit for drugs with particular value to society. This would entice companies into developing drugs that the government feels are of utmost importance, such as new drugs for tuberculosis or addictions. If the government concurrently passes legislation to limit price increases on marketed drugs, CRADA agreements might turn into very attractive commodities.

Mr. Chairman, years ago when as a housewife I was first introduced to the pharmaceutical industry, it was a rude awakening. I was trying to save my son from a lifetime of horrendous disability when I found out that no one would manufacture the drug that helped him because it would not be profitable enough.

This year marks the 10th anniversary of the Orphan Drug Act, and in the intervening years I have experienced a turbulent relationship with the industry that reflects the mutual dependency between patients and manufacturers. The fact is we cannot make these treatments ourselves; only the industry can make them for us. Our lives depend upon their compassion, their talents and their resources, and they depend upon the bottom line. But many drug companies have yet to realize that they can not survive without us, their customers. And we can't afford to buy drugs that are unaffordably expensive.

Although I have seen serious abuses, I have also seen extraordinary models of corporate responsibility. I have also met some of the most compassionate and caring individuals in corporate America. Believe it or not, we do recognize that the industry must be profitable in order to develop the drugs we so desperately need. It is vitally important that the government assures these companies that they won't lose money developing drugs under federal partnerships, and that they will make a reasonable profit. But if the government regulates utilities because they are a necessity of life, how can you not regulate the prices of drugs which are the difference between life and death to millions of Americans?

The American drug industry is much more than its trade groups represent, and there are many manufacturers who don't belong to trade groups. Indeed, in 1989 the National Commission on Orphan Diseases reported that more than 70% of CRADAs went to small and medium sized drug companies, but today NIH says that 45% of CRADAs go to large PMA companies. The industry, Mr. Chairman, is not homogeneous; there will be hungry companies willing to negotiate with the government about prices, and they will be delighted to sign CRADAs.

Since the rest of the industrialized world controls the prices of prescription drugs, we the American consumer and taxpayer, cannot continue to pay the price tag for the rest of the world's drug development. We may have evolved into the policemen of the world, but we can't continue to be the dupes of the world.

Whether we are paying our taxes or our health insurance premiums, we're all in this together -- we're paying for each other. It is time that manufacturers of government subsidized drugs are required to charge "reasonable prices" that give them the "reasonable" profits which they fully deserve -- no more and no less. It is the government's challenge to determine what "reasonable" prices are, and what a reasonable return on investment should be for manufacturers as well as taxpayers.

Thank you.

OTA TESTIMONY

Statement of

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and

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Office of Technology Assessment

Before the

House Committee on Small Business
Subcommittee on Business Opportunities, Regulation, and Energy

On

The Development of Ceredase™ and Its Implications for NIH Technology Transfer

January 25, 1993

Congress of the United States
Office of Technology Assessment
Washington, DC 20510-8025

I am Dr. Alan Garber, Health Service Research and Development Senior Research Associate at the Department of Veterans Affairs Medical Center Palo Alto, Assistant Professor of Medicine at the Stanford University School of Medicine, and principal contractor for a recent OTA background paper on the development of the drug Ceredase™, a costly treatment for the rare condition Gaucher disease.[1] Accompanying me today is Dr. Michael E. Gluck, Senior Analyst in the OTA Health Program who directed this background paper at OTA. We are here today to describe the involvement of NIH in discovering and developing this drug and to comment on what this case suggests about the role of NIH in insuring a fair price for drugs developed with substantial Federal assistance.

Gaucher disease is an inherited disorder in which the body lacks an enzyme necessary to break down glycolipids, substances produced by white blood cells. By accumulating in the body, these glycolipids can cause bone and abdominal pain, anemia, disability, and even death. Between 2,100 and 11,000 people in the United States are believed to have symptoms severe enough to warrant medical intervention.

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1. I am appearing before the committee today at the request of the Office of Technology Assessment and not the Department of Veterans Affairs. My views do not necessarily reflect the position of the VA. I am giving my testimony as a private citizen and as a contractor for OTA, not as a VA official.

Ceredase™ is the brand name for alglucerase, a chemical derivative of the missing enzyme and the only effective treatment for Gaucher disease. The Massachusetts pharmaceutical firm, Genzyme, Incorporated, manufacturers Ceredase™ as a Federally designated orphan drug entitling it to seven years without competition from other manufacturers.

Although the development of Ceredase™ predated current technology transfer policies at NIH, it was very much the product of NIH research. In the 1970s, researchers at the National Institute on Neurological Disorders and Stroke (NINDS)[2] identified the enzyme defect that causes Gaucher disease. In 1975, NIH received a patent for a method of harvesting the enzyme from human placentae (Patent Application No. 451,300). By the early 1980s, NIH researchers had chemically modified the enzyme to make it into an effective treatment. Furthermore, NIH organized, funded, and conducted the clinical trials that were central to the FDA's approval of the drug in 1991. NIH continues to conduct clinical trials to help determine optimal dosing strategies for Gaucher patients.

Between 1976 and 1981, NIH contracted with the New England Enzyme Center at Tufts University to supply NIH with sufficient quantities of the enzyme for its laboratory research. This piece of the Federal investment totalled almost $1 million. In 1981, Genzyme, then a new firm whose founders included researchers from the New England Enzyme Center, took over the contract to supply the enzyme. Over the next 11 years, NIH contracts with Genzyme totalled $9 million.

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[2] Between 1975 and 1988, this institute was known as the National Insitute on Neurological and Communicative Disorders and Stroke (NINCDS).

These contracts represent the formal relationship between Genzyme and NIH, although both parties indicate that they have collaborated and communicated informally over the years. As mentioned above, NIH received a patent that expired in 1992 covering a method of harvesting the enzyme from placental tissue. NIH never licensed this patent, and OTA was unable to determine whether this technology is at all relevant to the process currently used by Genzyme to produce Ceredase™.

NIH contributed to the discovery and development of this drug in two ways. The first was a direct dollar investment of $10 million in contracts to Genzyme. The second consisted of research by NIH scientists, as well as scientists at universities and private research institutions who received support from NIH. Over a period of decades, NIH paid for salaries, equipment, supplies, and overhead that were part of the research effort leading to the development of Ceredase™. Although clearly substantial, the dollar value of the latter contribution is unknown, because NIH accounting systems do not allow estimation of spending on specific research projects conducted in its own laboratories.

NIH's investment also reduced the risk borne by Genzyme that the drug would not prove safe and effective. By identifying, synthesizing, and conducting most of the early testing of Ceredase™, NIH in effect increased the probability that each dollar invested by Genzyme would yield a return. Although the exact risk of failure that Genzyme bore cannot be quantified, it is fair to conclude that is was substantially less than that faced by the average pharmaceutical firm deciding whether to pursue a promising R&D lead.

On the basis of information supplied by Genzyme, OTA estimated that Genzyme spent $29.4 million in R&D for Ceredase™ during the decade leading up to its approval by the FDA. This figure represents only cash outlays and does not include opportunity cost of money tied up in this investment during the period before it started generating revenues for Genzyme. In order to estimate Genzyme's fully capitalized R&D investment that includes this opportunity cost, we would have had to have known the timing of each cash outlay made by the firm. Genzyme continues to invest in R&D for Gaucher treatments. Clinical trials are currently underway for a genetically engineered form of the drug that would potentially be both cheaper to produce and safer for patients.

Prior to FDA approval, revenues from the sale of Ceredase™ partially offset Genzyme's R&D costs. Under the Treatment IND program, which makes promising experimental treatments available for otherwise untreatable conditions, manufacturers may offer unapproved treatments for a fee. The manufacturer is allowed to charge a price high enough to recover costs associated with the R&D and provision of the drug. As part of this program, the FDA allowed Genzyme to manufacture and sell Ceredase™ to patients not enrolled in clinical trials between the years 1989 and 1991, before full marketing approval. Genzyme received revenues from patients and their insurers through the Treatment IND program of between $5 and $6 million.

Ceredase™ is an extremely expensive pharmaceutical. While the total cost for the drug depends on the dosage administered, we estimate that this treatment can run from a minimum of $70,000 to more than a half a million dollars each year. Patients receive the drug for their entire lives. This high price may reflect relatively high manufacturing, marketing, and distribution costs, which we estimate to be $1.90 per unit in 1992. The drug's retail price is $3.50 per unit.

Ceredase™ is so expensive that many patients who receive the drug will risk losing their health insurance. Most patients with Gaucher disease have private insurance; according to data supplied by Genzyme, 73 percent of patients receiving Ceredase™ in March 1992 had private health insurance that covered their therapy, usually with out-of-pocket expenses of less than $2000. Another 21 percent were covered by Medicare or Medicaid. While Medicare itself covers only 80 percent of the costs associated with treatment, most Gaucher patients with Medicare coverage also have supplemental private health insurance to cover the remaining 20 percent. Medicaid pays virtually all costs associated with Ceredase™.

Because the vast majority of private health insurance plans place a limit on the lifetime benefits payable for an enrollee, OTA estimates that somewhere between one-third and one-half of all Ceredase™ patients face a significant risk of exhausting or critically reducing their available insurance benefits over time. Although Genzyme provides the drug free to patients who exhaust (or otherwise lack) health insurance, these patients lack coverage for the cost of administering the drug (which is done in a physician's office) and any other medical expenses they incur for the rest of their lives. These patients would face serious obstacles to obtaining private health insurance after exhausting their existing benefits. Some potential insurers may exclude their Gaucher disease treatment as a preexisting condition. Other patients may have trouble getting new insurance by changing jobs if potential employers are reluctant to hire individuals who are expected to have unusually high health expenditures.

You have asked us to comment on some of the policy implications of Ceredase™. There is no doubt that in terms of reaching the goal of transforming NIH research results into commercial products, Ceredase™ is a success. However, in asking whether this project served the public interest, we must consider a broader set of issues. In particular, because most patients have health insurance policies that pay for all but a small fraction of the charges for covered drugs and other health care products and services, they may be willing to "purchase" such care even when it is worth less to them than what the seller charges.[3] Because the patient bears only a fraction of the costs, commercial success for a health product does not mean what it does in other markets. For most other goods and services, the purchasers spend their own money, not that of a third party.

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[3] Privately insured patients do pay insurance premiums that provide the revenues insurers use to reimburse for drugs and other covered medical expenses. Once they have insurance, however, they have no incentive to take into account the price of a drug when they purchase it. The relevant price to the insured patient is the fraction of the price not covered by insurance.

Of course, commercial success would be elusive if insurers were not willing to pay for this drug. Insurers have little flexibility in choosing what pharmaceuticals they cover and what prices they will pay. Virtually all private insurance contracts with prescription drug benefits agree to cover any medically-indicated FDA-approved pharmaceutical. Medicaid now also pays for almost every drug approved by the FDA. While Medicare usually does not pay for drugs administered on an outpatient basis, it pays for Ceredase™ because the drug is administered as an intravenous infusion under a physician's supervision.

The extensive insurance coverage of Ceredase™ means that patients pay only a fraction of charges for the drug. Insurers, insofar as they are unable to deny coverage for a unique nonexperimental drug, are forced to pay what the company charges. If there were competing producers of the drug, it might be possible to obtain the drug at lower cost, but Genzyme's seven-year market exclusivity awarded under the Orphan Drug Act eliminated such competition. High prices are inevitable when a profit-making firm has a monopoly in the production of a drug and when insurers must pay for it, regardless of price.

When the Federal government has transferred technology from its own laboratories to private firms, and when, as in the case of Ceredase™, it pays for the drug again through public health insurance programs like Medicare and Medicaid, the government has an incentive, indeed responsibility, to examine the price closely and perhaps act where the market itself or other insurers cannot. This responsibility is the basis for the fair pricing clause in NIH's current licensing policy.

What lessons does our review of the costs of developing and providing the drug Ceredase™ hold for any attempt by the Federal government to analyze of fairness of prices charged for drugs that result from licensed NIH technology?

Although the concept of fair pricing is subject to differing interpretations, it seems that the term is commonly used to mean that the price charged does not greatly exceed the cost of researching, developing, manufacturing, and distributing the drug. As our experience in studying the costs of developing and providing the drug Ceredase™ suggests, determining such costs is a difficult and serious task. Any attempt to analyze costs associated with drugs resulting from licensed NIH technology is likely to face challenges like those we encountered. The capacity to conduct such an analysis will require relevant expertise.

Such expertise is particularly important because there are many areas of uncertainty and controversy in estimating R&D and manufacturing costs. Any organization that attempts to conduct such analyses will need professional staff with expertise in corporate accounting and economics, among other areas. Even though the scope of our inquiry into the costs of developing and manufacturing Ceredase™ was limited, we found that it was important to ensure input from both economists and accountants.

Implementing a fair pricing clause is not a straightforward exercise, and the implicit limits on pricing may ultimately conflict with NIH's goals of technology transfer and the collaborative development of new medicines with industry. When faced with additional scrutiny, some firms may opt not to license drug technology developed at NIH. The validity of this fear will only become apparent with time.

The public investment in biomedical research is substantial. NIH research results promise to bear valuable fruits. In doing so, however, concerted effort will be needed to protect the public interest. Enforcement of the NIH's fair pricing clause will require the expertise to determine the relationship between a drug's price and cost. Such analyses may also have the added benefit of clarifying some of the broader public debate about pharmaceutical pricing and profits.

HEARING STATEMENT

DR. STEPHEN W. SCHONDELMEYER
PROFESSOR
COLLEGE OF PHARMACY
UNIVERSITY OF MINNESOTA

January 25, 1993

BEFORE THE SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES AND ENERGY

Good morning Mr. Chairman. My name is Stephen Schondelmeyer, and I am a professor of Pharmaceutical Management and Economics at the University of Minnesota.

Since 1980 I have been involved in a number of funded research projects assessing pharmaceutical pricing trends. I have worked on a number of reports to Congress regarding this issue, and have cooperated with research agencies including the National Institutes of Health, the Health Care Financing Administration, the Office of Technology Assessment and the U.S. General Accounting Office.

Currently, I am assisting the GAO in an analysis of pharmaceutical prices requested by your subcommittee. The GAO hopes to complete that project sometime this spring.

You have requested that I respond to several issues raised in the development of the current model cooperative research and development agreement (CRADA) used by the National Institutes of Health in co-development arrangements with private drug companies.

Your questions center on the efficacy of reasonable and fair drug pricing language in the model CRADA, and I understand that that language is of particular interest to you in the co-development of the anti-cancer drug, Taxol.

The core of your concern is whether the NIH, or any of its constituent laboratories, can properly exercise this portion of the agreement absent (1) the development of specific expertise to assess the technical cost and competition elements in determining a price, or (2) the cooperation of its private partner who must disclose data in order for a determination to be made.

As I understand the process in the Taxol agreement, and in most CRADAs, Bristol-Myers does not feel legally bound to bring forward information, and NIH does not feel it has authority to compel it. Consequently, despite the language in the CRADA agreement NIH can not adequately assess whether a fair and reasonable price has been set.

Your questions concern whether this environment serves the public interest. Should the federal labs play a more active role in determining the fairness of a price set on a co-developed drug such as Taxol, or a number of other pharmaceuticals which recently have been the subject of controversy and debate in this regard?

I see two essential issues:

First, is the CRADA itself, including language stating that NIH reserves the right to determine if there's a reasonable relationship between price and the public's investment in a product.

At this point, it appears that NIH has done little more than accept Bristol-Myers' word that this price is reasonable. There does not seem to have been any detailed assessment of either cost of research and production, or relative market value. Bristol-Myers and other pharmaceutical companies have argued that these are very complex decisions. Indeed, I agree with that assertion. However, pharmaceutical companies routinely make business decisions in these complex areas when they purchase the license of a product from another company, or even a public sector university. Also, financial analysts routinely make pricing and revenue projections in this same complex environment.

Second, drug companies customarily deal with universities and other companies to acquire innovative products and bring them to the market. These business relationships almost always include a royalty and/or a lump sum payment.

If the board at NIH was a private corporation advising their scientists to license valuable intellectual property without some form of remuneration such as a royalty or lump-sum payment, or in this case adjusted pricing to account for these values, the stockholders of this private corporation would be up-in-arms against the board.

In fact, Bristol-Myers has purchased such innovations from other sources in their efforts to capture a synthetic or semi-synthetic Taxol analog.

There is no reason why a government agency that develops valuable property should not recover at least part of the value of their innovation. There is no reason why recovery, or return on that investment, could not be in the form of a more restrained price benefitting taxpayers and consumers.

You ask if some agency of government needs to establish and use expertise in making determinations in this area.

Definitely the expertise is needed. The question is where, and how much, and whether there are other related functions that need to be performed as well as this one. For example, HCFA through both Medicare and Medicaid will be paying for a substantial share of the Taxol that is purchased in the U.S. Therefore, HCFA also needs to conduct an assessment regarding what is a reasonable and fair price for Taxol, as well as for other drugs developed and marketed through CRADAs or under other government support.

The equivalent of a Canadian Patent Medicine Price Review Board, which monitors the rate of change in existing prices and assesses the appropriateness of initial prices for drug products introduced in Canada. In fact, the Canadian Parliament is currently considering legislation to strengthen the authority of this review agency. Most industrialized countries have a government agency that either monitors or sets the price or profits of pharmaceutical products. Such a review body in the United States would give the government the kind of expertise and data that is needed to reach judgments on the fairness and reasonableness of drug prices.

This type of expertise is needed not only for developing licensing agreements, but also to assist the government in purchasing pharmaceuticals. Collectively, federal and state governments are estimated to pay for 35 to 40 percent of all prescription pharmaceuticals.

Mr. Chairman, this kind of pricing review could play a significant role in slowing the rate of growth in health care spending. American's spend about $59 billion per year for prescription drugs in 1992.

Mr. Chairman, I realize that these pharmaceutical companies are not anxious to disclose this data, and that they have threatened to abstain from further cooperative research with federal labs if we require them to reveal some of these numbers, even in a confidential way.

In my view, while these companies feel threatened by this request we are asking no more of them than this government asks of major defense contractors when we determine the price of new weapons technology. Again, if an adequate degree of confidentiality is maintained, disclosing the data you need would pose no undue burden on the drug companies. The American public has every right to expect oversight and accountability where their tax dollars are concerned.

STATEMENT OF
ELLEN STOVALL
EXECUTIVE DIRECTOR
THE NATIONAL COALITION FOR CANCER SURVIVORSHIP
BEFORE THE
COMMITTEE ON SMALL BUSINESS
UNITED STATES HOUSE OF REPRESENTATIVES

JANUARY 25, 1993

Good morning, Mr. Chairman and distinguished members of the Committee. My name is Ellen Stovall. I am Executive Director of the National Coalition for Cancer Survivorship—the largest national organization advocating on behalf of people with all types of cancer. NCCS members include hundreds of grassroots cancer organizations including The National Breast Cancer Coalition, US-TOO, The Candlelighters Childhood Cancer Foundation, The American Cancer Society, and most of this country's leading cancer treatment institutions. Our most important constituency are the more than 8 million people living in the United States today, including myself, who have received a diagnosis of cancer.

Of utmost concern to NCCS and its members is the urgently-needed reform of our health care system which would allow for access to state-of-the-art cancer treatment for all Americans. Based on health status alone, people with cancer experience discrimination and are largely denied access to coverage under the guise of "preexisting conditions." This unacceptable practice must be eliminated by any reform of our health care system and NCCS recognizes a responsibility to approach this reform with measures that address the inevitable cost-containment components. We are concerned, however, with any regulations or reforms toward cost-containment that would fail to acknowledge the necessity for comprehensive, high-quality cancer services.

Like people with AIDS and other chronic and life-threatening illnesses, people living with a cancer diagnosis frequently must face the fact that there is no known cure for their illness. Until more is known about the prevention and control of cancer, our greatest hope lies in the discovery and development of new anticancer agents. Our collective efforts toward expanded availability to health care are futile if we cannot offer our citizens access to the most advanced medical technology in the world. We heartily endorse any initiative—public, private or collaborative—that will increase the prospects for cancer survival.

NCCS appreciates this Committee's interest regarding the fair pricing clauses of drugs developed under Cooperative Research and Development Agreements (CRADAs). We commend this Committee for its efforts to act in the public interest to ensure that collaborators in these agreements perform responsibly in the pricing of products. As you know, CRADAs offer one of the most promising mechanisms for the public and private sector to cooperate in bringing new drugs to market and we urge you to do everything you can to assure that this cooperative arrangement can thrive and bring promising new treatments like Taxol to the public in the most expedient manner possible.

NCCS currently does not support or discourage the use or promotion of any particular cancer treatment. Moreover, we are not experts in the regulatory process which sets standards and pricing for drug development and marketing. We feel very strongly, however, that when this world's preeminent cancer research institution, the National Cancer Institute, lauds the new therapy, Taxol, as the most important one developed in the last decade, and that the process by which it has come to market may be jeopardized by politicizing the pricing practices, we must speak up!

You requested us to address whether restrictive pricing enforcement might discourage collaboration between the government and private sector. We feel very strongly that it would, and we could not support any regulations—pricing or otherwise—that create disincentives of any kind to industry in cooperative development of new agents discovered through federally-funded research. Furthermore, NCCS has been very involved in working with other coalitions to increase funding for cancer research, and through that process we have become painfully aware of the lack of adequate NIH funding to carry forth the promising basic research that will result in new treatments for cancer. We are very concerned that to burden the Institute with laborious and detailed pricing evaluations would result in taking away valuable time and resources from what we feel should be its main emphasis—the precipitous development of new products that will add measurable quality to the lives of people living with this devastating illness that will strike one in three Americans and kill one in four. We know you, particularly, Congressman Wyden, have been most supportive of very important legislation that effects the health of the American people. You and your esteemed colleagues in Congress can make a real difference for all of us living with this diagnosis by encouraging the development of new products and by fashioning a health care delivery and reimbursement system that provides for universal access to that system.

My cousin, Sally Roos Schneck, who is living with a diagnosis of ovarian cancer and is alive today only because of Taxol, has traveled a long distance to be with me to witness these proceedings. She wrote you last week and I ask that you consider allowing her to say a few words to the Committee. Thank you very much for the opportunity to appear before you to address our concerns. I would be pleased to answer any questions.

Statement of Peter S. Arno, Ph.D.

Associate Professor
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before the

Subcommittee on Regulation, Business Opportunities, and Energy
of the
Committee on Small Business
U.S. House of Representatives

Washington D.C.

Monday, January 25, 1993

Good morning, Mr. Chairman and members of the committee. My name is Peter Arno and I am a health economist and associate professor in the Department of Epidemiology and Social Medicine at Montefiore Medical Center and Albert Einstein College of Medicine in the Bronx. It is a privilege to be here today.

As health care reform moves to the top of the national agenda, this committee is taking a bold step in examining the pricing practices of the drug industry. In my mind, your mission will best be served by seeking answers to two crucial questions. First, what is the fairest way to commercialize therapies when the government has played a major role in their research and development? And second, what is the best way to ensure that any pharmaceutical product is reasonably priced?

The "reasonable pricing" clause now included in the federal government's Cooperative Research and Development Agreements (CRADAs) with private industry is a modest first attempt at injecting oversight into the marketing process. The background to this clause is worth noting. You may recall that National Cancer Institute scientists and federal funding played pivotal roles in the development of AZT as a treatment against AIDS. The government then granted double monopoly protection to the Burroughs Wellcome Company in the form of exclusive marketing rights both under the Orphan Drug Act and from the United States Patent and Trademark Office. Because of this, the government had no means of asserting control over the outrageous price the company promptly slapped on the drug. For that, the government has paid dearly. Millions of dollars have been diverted from the Medicaid and Ryan White programs over the past five years to subsidize the cost of AZT for those who could not otherwise afford it.

To prevent that debacle from recurring, officials at NCI began to insist that a reasonable pricing clause be inserted into exclusive licensing agreements for drugs developed in public-private partnerships. Unfortunately, the terms in these CRADA contracts are vague and unenforceable. That was apparent when the first "reasonable pricing" requirement was imposed on the license for ddI given to Bristol-Myers in January 1988 and it is apparent today, as public outrage builds over the price of Taxol, for which Bristol-Myers Squibb received exclusive licensing rights in January 1991.

The contractual language of the reasonable pricing clause requires the manufacturer to provide evidence that there is a relationship between the market price of the drug and the health and safety needs of the public. In the case of Taxol, the company must also show that there is at least some relationship between pricing and the extent of the public investment. What, exactly, does this mean? What information did Bristol-Myers Squibb have to provide the government to gain its monopoly on Taxol? The answers have not been made public; this would be an appropriate avenue of inquiry for this committee.

It is apparent to most observers that the reasonable pricing clause needs more teeth. In order to establish a fair price for a pharmaceutical product that has been developed jointly by the government and the private sector, much stricter standards must be established. This requires the company to disclose, in confidence, information that is currently considered proprietary. At a minimum, this should include the following data:

- Development costs.
- Marketing and distribution expenses.

- The presence and prices of similar competing therapies.
- The likelihood and timing of market entry for additional competing products.
- The projected time it will take to recover development costs.
- The profit margin that has been built into the price.

Purportedly for competitive reasons, the drug industry is extremely reluctant to sketch this financial picture. However, an agency of the federal government with economic and accounting expertise could appropriately collect and analyze this data in a confidential fashion. The National Institutes of Health is certainly capable of assembling the expertise needed to perform these functions but the assignment would go beyond the purview of its scientific mission. The Health Care Financing Administration may be a more suitable agency for the task.

Would these disclosure requirements be so onerous that drug companies would choose not to participate? Some may opt out. However, it is unlikely that all companies would refuse to participate in CRADAs, despite what a chorus of industry lobbyists might now say. Given the vast amount of basic and applied biomedical research conducted by the federal government and the intensely competitive international pharmaceutical marketplace, there should be no shortage of companies who are willing to collaborate with the government.

Let me turn now to a somewhat bolder approach to the control of drug pricing. If the government, at taxpayer's expense, has contributed significantly to the development of a new drug, why confer a monopoly on a private company at all? Whether it is done through the mechanism of an exclusive licensing agreement or with a patent, the economic rationale seems slender indeed. Nor is a monopoly necessarily in the public interest.

Three strong arguments can be made against a government-granted monopoly.

First, in economic terms, a monopoly price is, by definition, higher than a competitive market price. That means that scarce resources are being misallocated and consumers are being held hostage to the marketing and distribution plans of a single corporation. The human consequences of high drug prices are wrenching — drugs become unaffordable to many individuals in need. For them, the industry's boasts about its record as an innovator are small comfort indeed.

Second, the likelihood that insurance coverage for pharmaceuticals will be broadened in the near future means that monopoly pricing will take income away from consumers and taxpayers and redistribute it to the pharmaceutical industry.

Finally, the use of public funds gives the government a moral obligation to ensure that products are justly priced and that they are accessible. By suspending the rules of competition, the current system of exclusive licensing or patent protection, interferes with this mandate.

At present, pharmaceutical companies are not regulated like other government monopolies, such as the public utilities. If the industry wants to operate in a competitive marketplace, then it should live by competitive principles. That means stripping away the artificial protection of government-granted monopolies. If it cannot or will not abide by competitive principles, then the public interest demands that its monopolies be regulated. Industry cannot be permitted to have it both ways.

I would argue that the federal government should grant private industry a monopoly only under two circumstances: 1) if it can be demonstrated that the monopoly pricing and profits are needed to offset an extraordinary investment that was required to bring a new drug to market or; 2) if the potential market for the drug is so small that no company is willing or able to invest the requisite resources in research and development. Under all other circumstances, the government should grant non-exclusive licensing agreements when it has been substantively involved in the development of a new drug. The resulting competition makes a lower drug price far more likely.

Neither of these conditions prevailed in the case of Taxol or a long list of other drugs, including AZT, pentamidine, foscarnet, erythropoietin, human growth hormone and many others. When Bristol-Myers Squibb was granted its license for Taxol, the government had already conducted or funded the lion's share of research and development. That meant the company's costs were far lower than average and its risk was minimized. Moreover, there is a distinct possibility of an expanded and much more lucrative market. Although the FDA licensed the drug for a limited population — women with ovarian cancer who had failed previous chemotherapy — it is widely recognized that Taxol is also a promising therapy for earlier treatment of ovarian cancer and for breast, lung, head and neck cancers. If research bears this out, stock analysts say it will be worth hundreds of millions of dollars annually to Bristol-Myers.

For the past ten years, our society has been trying to come to grips with containing health care costs. Now this has become an imperative. Two independent commissions have been chartered to advise Congress on how to contain expenditures in the two largest segments of the health care market. The Prospective

Payment Commission (PROPAC) has been impaneled to review hospital costs and the Physician Payment Review Commission (PPRC) is studying the price and value of physician services. Yet the fastest growing component of health care costs — pharmaceuticals — remains exempt from administrative oversight. In most industrialized countries of the world, some form of control over drug prices is automatic. We ought to do no less for American citizens. It is long past time to make this issue a central part of the dialogue about national health care reform.

Would this sound the death knell for innovation in the pharmaceutical industry? The answer is clearly no. To understand why, we must question at least two assumptions that the pharmaceutical industry has ingrained in the public consciousness. First, in endless advertising and lobbying campaigns, the industry claims that its innovative accomplishments are unsurpassed. Yet between 1985 and 1990, more than 80 percent of all new, FDA-approved molecular entities showed only modest or little therapeutic gains over drugs that were already on the market. Second, the industry is quick to claim that its substantial investment in research and development adequately justifies the high and rising price of drugs. Yet it remains silent when asked to document the exact nature of its expenditures or to explain why more money is spent on marketing and advertising than on R & D.

In conclusion, let me reiterate two key points. The reasonable pricing clause inserted in CRADAs will have little meaning unless the drug industry is mandated to disclose actual costs and projected profits. However, a more effective and simpler approach to price controls is the elimination, under most circumstances, of government-granted monopolies. Given the constraints of a free enterprise system, competition should be allowed to rein unless there is good cause to take another approach.

Finally, I would like to commend this Subcommittee for its willingness to take on the tough issue of the pricing practices of the drug industry. Your efforts to transform the process of technology transfer so that it better serves the public interest are sorely needed and warmly welcomed. Hopefully, these issues will remain on the table as Congress and the new Administration pursue systemic reforms in the health care system during the coming months.

Thank you.

Statement
Pharmaceutical Manufacturers Association

ROBERT F. ALLNUTT
EXECUTIVE VICE PRESIDENT
PHARMACEUTICAL MANUFACTURERS ASSOCIATION

BEFORE THE

COMMITTEE ON SMALL BUSINESS
SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND ENERGY

UNITED STATES HOUSE OF REPRESENTATIVES

JANUARY 25, 1993

I am Robert F. Allnutt, Executive Vice President of the Pharmaceutical Manufacturers Association. PMA represents more than 100 research-based pharmaceutical companies that discover, develop and produce most of the prescription drugs used in the United States, and a substantial portion of the medicines used abroad. I appreciate the opportunity to appear before the Subcommittee today to present the industry's views on cooperative government-industry drug development efforts and specifically on Cooperative Research and Development Agreements (CRADAs) between PMA member companies and the National Institutes of Health (NIH).

GOVERNMENT LICENSING AND CRADAS

As the Subcommittee knows, over 90% of new medicines brought into use in the United States are discovered, tested, developed and produced by the private sector. However, from time-to-time important new therapeutic approaches are discovered by NIH scientists, under NIH grants, or through collaborative efforts with private sector scientists. For many years now, the NIH has encouraged the research, development and eventual marketing of promising new therapies first discovered in research sponsored by NIH by relying on the cooperation and proven capabilities of research-based pharmaceutical companies. In the Stevenson-Wydler Act of 1980, and again in the Bayh-Dole Act of 1986, Congress reaffirmed this reliance by authorizing exclusive patent license agreements with the private sector and by authorizing federal entities to enter into CRADAs with industrial organizations.

Moreover, during the 1992 Presidential campaign, President Clinton repeatedly called for increased cooperation between government and industry to spur the development of new technologies. For example, in his September 21, 1992 paper on Technology: The Engine of Economic Growth, President Clinton stated, "A Clinton-Gore Administration will work to build a productive partnership between government, research labs, universities, and business."

The 1986 Act recognizes that exclusivity is a powerful incentive to private investment in the research and development necessary for the results of government research to reach patients as new products. PMA believes that in general the 1986 Act is working quite well, as are NIH's licensing and contractual policies consistent with that Act and the Stevenson-Wydler Act.

CRADAs generally focus on early research activities such as screening compounds, developing receptor technology and conducting other research drug-discovery activities. At this early stage, government and corporate researchers can collaborate to identify and pursue research leads. Normally it is not the role of the government to develop a compound that results from this collaboration into a commercial product. This development activity includes toxicology testing, formulation and clinical testing, followed by extensive interaction with the Food and Drug Administration. These activities usually are the responsibility of the corporate "partner". Under NIH policy, the government is usually compensated for its role in the early research of the patented drug by a royalty. The amount of the negotiated royalty is based upon a number of factors including the degree of risk assumed by the corporate partner. Obviously, the risk of successfully completing all these steps following discovery of a potential new therapeutic is very high.

As NIH officials have stated, government agencies and laboratories have neither the capability nor the expertise to undertake and manage the massive clinical trials and other work necessary to develop and obtain approval for new drugs and, after approval, to produce, market and distribute commercial quantities of final dosage-form products for patients.

The goal of government licensing and research policies obviously must be to encourage the participation of private entities if product-specific discoveries which sometime emerge from that research are to be developed into new therapies for patients. If these policies fail, for whatever reason, to achieve this goal, potential therapies will not be commercialized as quickly as possible or perhaps may never be made widely available to treat disease.

CRADAs WITH THE NATIONAL INSTITUTES OF HEALTH

For the information of this Subcommittee, on December 21, 1992, PMA responded to a series of questions raised by President-elect Clinton's Healthcare Transition Team regarding the role of the government in new drug research and development, including CRADAs. The questions and PMA's responses are provided below.

TRANSITION TEAM QUESTIONS AND PMA ANSWERS

Q. *In light of recent interest in the issue of the pricing of drugs developed whole, or in part by Federal laboratories, what are the industry's thoughts on the best mechanism to address the issue of the pricing of these products?*

Q. *Can the industry help develop a cost accounting methodology to determine the actual dollar contribution of the Federal government to the basic and clinical research on new drugs so that the price reflects that investment?*

Q. *What are some mechanisms that can be used, other than NIH, to negotiate prices of drugs developed through Cooperative Research and Development Agreements (CRADAS)?*

Q. *What are some mechanisms that can be used to retain the incentive for drug manufacturers to enter into CRADAS with NIH?*

PMA supports the basic position adopted by NIH in favor of awarding exclusive rights in appropriate circumstances to private entities so that the incentives of our patent laws can best be brought to bear on the commercialization of new compounds first isolated in government laboratories. In general, the Technology Transfer Act of 1986 is working well, as are the NIH licensing policies consistent with that Act.

Several leading PMA companies have entered into CRADAs with NIH, while others have declined to enter such agreements. In order to retain this important cooperation between government and industry, the Administration should seek to avoid creating any additional disincentives to technology transfer.

A company which undertakes commercialization of the product must have adequate free-market incentives to do so. Without private industry support for these products, they would not be made available to the public. Strong consideration of the risks involved with bringing a new product to market must be factored into any such review. But the government may have a legitimate claim to compensation due to their collaborative efforts. Both the level and mechanism for such compensation depend on the extent of the government's role in R&D, and perhaps on the government's role in distributing products, such as in substance abuse treatment programs.

Given the variability in the government's role in product development and distribution, no simple answer is possible. Within the context of antitrust laws, PMA would be willing to work with NIH to identify incentives for CRADAs and develop appropriate principles or models for compensation of government contributions.

The Subcommittee's December 17, 1992, invitation to testify requests that PMA respond to various questions regarding pricing provisions currently used in NIH CRADAs, particularly with respect to the agreement to develop and market the newly approved anti-cancer drug, Taxol. Beyond observing that the Taxol situation involves a number of unique features that differ from the more traditional CRADA efforts, PMA cannot appropriately comment on the negotiations between the company and the NIH on this new pharmaceutical. The Association has had no role in the negotiations with NIH regarding the development and commercialization of any new drug, including Taxol. However, we do offer the following responses with respect to the questions posed in the Chairman's December 19 letter.

> *"If [pricing] information is not being made available because of a lack of statutory authority, should the NIH request such authority from Congress? If not, why not?"*

The 1986 law authorizing CRADAs makes no reference to inclusion of pricing provisions in such agreements. I understand that in practice, federal agencies, other than NIH, have chosen not to include a pricing clause in their agreements. NIH as a matter of contract has elected to include a pricing provision in its CRADAs and in individual patent license agreements. We are not aware of any need to provide additional legislative authority in this area.

> *"What should be the federal government's position regarding restraint on the pricing of drugs which are co-developed through CRADA similar to the Taxol development program?"*
>
> *"It is unclear exactly how the federal partner will arrive at a conclusion that the drug's price is fair and reasonable. Please explain the process as currently envisioned by the drug manufacturing industry in this regard."*
>
> *"In your view, does the model CRADA provide the NIH access to [pricing] information, even on a confidential basis?"*
>
> *"If NIH declines to request [pricing] information, or the statutory authority to demand it, how could the NIH otherwise expect to enforce fair and reasonable pricing provisions of the model CRADA?"*
>
> *"In your view, should the fair and reasonable pricing provision of the model CRADA be excised? If not, why not?"*
>
> *"Should fair pricing language be strengthened? If so, how so?"*

The model pricing provision developed by NIH for CRADAs is properly phrased in somewhat general terms. Under it, NIH may require the CRADA partner to support by reasonable evidence the relationship between the pricing of the licensed product, the public investment in that product, and the health and safety needs of the public. This does not permit NIH to set or dictate prices for licensed products. This general provision allows both NIH and the CRADA partner to negotiate regarding pricing information, if that is their mutual desire, based on the circumstances of the particular product in development.

> *"Please describe your understanding of the expertise -- or the lack thereof -- now being used by NIH labs in determining that the fair and reasonable price provisions of CRADAs are being enforced. Should the federal labs develop a stronger drug price assessment capability, and if not why not?"*
>
> *"Please respond to the suggestion that Bristol-Myers Squibb accept the creation of an expert panel at NIH which could -- on an utterly confidential basis -- evaluate minimal drug development cost data necessary to the analysis of the fair pricing clause in the pricing of Taxol, and afterwards render a report to NIH managers."*

NIH states that it does not have specific price assessment capabilities. As we do not believe NIH should be in the price regulation business, we would oppose the establishment of additional price assessment capabilities within NIH as unnecessary and counterproductive. The overriding government goal should be to encourage companies to enter into cooperative agreements to bring promising new compounds to patients. This objective could clearly be compromised if the government becomes more involved in reviewing, second-guessing or challenging a company's pricing determinations for individual products. Additional government involvement in pricing would not only be unwise public policy but also a misuse of limited NIH resources. Pricing decisions are far more complex than simply reviewing development cost data -- itself a complex task -- and we do not view creation of the panel and process suggested by the question as appropriate or necessary.

> *"Please discuss possible problems posed by more restrictive pricing language. For example, how real is the threat that drug manufacturers will pass up potentially lucrative joint ventures with NIH because of a reluctance to provide cost data they presently consider proprietary?"*

PMA does not become involved in individual company determinations regarding CRADAs. Several PMA companies are CRADA collaborators. We are aware that NIH representatives have testified that other research-based companies have declined to enter into CRADAs because of concerns over pricing clauses. Successful companies are not limited in their future R&D investment choices to a single project or family of therapies. A particular company, in determining how best to invest its research and development dollars, may well choose to put its resources into projects that do not raise the probability of government agency access to internal pricing information and protracted public proceedings about pricing decisions.

There are several additional points that should be noted by the Subcommittee in considering NIH licensing policies. First, the terms of an exclusive license are to "fairly reflect the relative contribution of the parties to the invention and the CRADA, the risks incurred by the collaborator and the costs of subsequent research and development needed to bring the invention to the marketplace." Royalty-bearing licenses are contemplated with royalty rates based on product sales. We understand that several NIH licenses require royalty payments to the government in those instances where the product being developed has a patent.

Second, NIH has control over which company is selected as a CRADA partner. There is no obligation that NIH enter into a CRADA or patent license with a company about which NIH has any appropriate concern. Third, NIH may contractually terminate an arrangement if a company breaches its contractual obligations, including those relating to pricing.

Finally, it is our belief that the best possible means of ensuring broad access to new therapies and fair and responsible pricing is to promote competition in the marketplace. NIH is already pursuing such a strategy by entering into CRADAs involving potentially competitive products developed by different companies.

Mr. Chairman, this concludes my prepared testimony. I welcome any questions you or any other members of the Subcommittee might have.

Pharmaceutical
Manufacturers
Association

Robert F. Allnutt
EXECUTIVE VICE PRESIDENT

March 17, 1993

The Honorable Ron Wyden
Chairman, Subcommittee on Regulation,
  Business Opportunities, and Energy
Committee on Small Business
U. S. House of Representatives
Washington, D.C.

Dear Mr. Chairman:

At the January 25, 1993 Subcommittee hearing on cooperative government-industry technology transfer you requested that PMA submit for the hearing record further details regarding the industry position that royalties paid to the Government may be appropriate where the licensed technology is patented.

The January 25 hearing explored the cooperative new drug development relationship between private industry and the National Institutes of Health under Cooperative Research and Development Agreements (CRADAs). PMA's position is that the contractual relationship between NIH and the private R&D collaborator, whether that relationship is in the form of a CRADA or a product license agreement, should generally be the same as if both parties were in the private sector. Thus, if the United States owns a U.S. patent or a patent application under which exclusive rights are available, the NIH and the private collaborator should mutually negotiate an exclusive license agreement which could be royalty bearing if both parties agree. Such an arrangement would preserve incentives for companies to enter into CRADAs and help avoid the disincentives inherent in the pricing clause currently in use.

The terms of the license would be individualized to the particular technology under development, and the license would reflect the contributions and resources that each party brings to the agreement and the developmental risks which are assumed by each party. The amount of the royalty and payment method, such as lump sum or royalties based on sales of the marketed product, would be determined by the parties to the agreement based on the particular circumstances relating to the invention.

A licensing arrangement of this type would enable NIH to receive a fair market value return on the governmental contribution to the creation of a new pharmaceutical product and

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thereby generate funds to support additional Federal research to identify new compounds and ultimately new drugs for patients. We note that the NIH Model CRADA agreement includes an option for the private collaborator to negotiate a royalty-bearing exclusive commercialization license consistent with the Federal Technology Transfer Act of 1986 and the 1980 Bayh-Dole Act.

PMA appreciates the opportunity to supplement the hearing record.

Respectfully submitted,

Robert F. Allnutt

The Hon Ronald Wyden (D-OR)
Chairman, House Small Business Subcommittee on Regulation,
Business Opportunities and Energy
U.S. House of Representatives,
Washington, D.C. 20515

Att. Steve Jenning FAX 2022258950

365 Millwood Road
Chappaqua, N.Y. 10514
(914) 666-2040
Jan.22, 1993

Dear Rep. Wyden:

12,000 American women are on death row. We are not murderers, pedophiles, rapists, yet we will die before the new year ends. And, in all likelihood, unless some miracle drug appears soon, 12,000 more women will die in '94. And '95. Unlike criminals, we cannot plea bargain or hope for a pardon: our death sentence stands firm. For some of us, there is a hope for a reprieve - not permanent, but the chance for "a little more time." which is all we can realistically hope for. And what is our crime, why do we face a tortuously agonizing death? We have ovarian cancer.

Though the bark from the Pacific yew tree was used medicinally by Natives Americans long ago, the extract known as taxol was isolated in 1963 under a grant by the NCI. Initial screening tests indicated potential as an anticancer agent, but research efforts lagged until a 1979 study showed taxol's unusual ability to disrupt and essentially halt the multiplication of certain cancer cells. Phase 1 trials of taxol began in 1983. In January, 1991 - nearly 28 years after its positive effects on rodent cancers was reported, and apparently disregarded - NCI entered an agreement with Bristol-Myers Squibb to provide trees, research and significant funds in exchange for NCI's clinical research data and what amounts to the exclusive right to market the drug for seven years. In October, 1991, after four major operations and three courses of chemotherapy, I was able to enter a Phase 2 taxol trial, offered at 39 cancer centers around the country, for "compassionate use." "Compassionate use" means you've run out of chances, the standard treatments won't work any more. I was one of the lucky ones: I was able to qualify for the study; I am still alive to attest to the efficacy of the drug. There are indications my remission is over: I've spoken with my oncologist at Memorial Sloane Kettering regarding receiving taxol again. The next remission will be shorter --there is no cure. Just a little more time. Even that sounds good to women like me.

Your committee has heard women testify regarding their illness and taxol. Please, please listen to more of us. It's 30 years since taxol was first isolated, only two years since the drug has been available to more than a few hundred of us. It shows promise for treatment of breast and lung cancer, malignant melanoma as well as ovarian cancer. It is the only drug thus far that offers any hope.

It would be difficult to argue that some drugs ~~are~~ aren't priced unfairly, that drug companies are not "gouging" in some - or many - cases. But surely your committee could find a test case that didn't seriously threaten accessibility, and life, to so many doomed women.

Please listen to our story before you decide that this particular CRADA funding - and the marketing of taxol - do not represent the taxpayers' interests. I'll attend your committee meeting on Monday, January 25. I have to be there, to represent myself and 11,999 others.

Yours sincerely,

Sally Roos Schneck

Sally Roos Schneck

c: Ellen Stoval FAX 3015659670
National Coalition for Cancer Survivership

TESTIMONY OF
BARR LABORATORIES
BEFORE THE
SUBCOMMITTEE ON REGULATION
COMMITTEE ON SMALL BUSINESS
U.S.HOUSE OF REPRESENTATIVES
JANUARY 25, 1993

Barr Laboratories is a manufacturer of generic drugs headquartered in Pomona, N.Y. In early 1991, representatives of Barr approached the National Institutes of Health (NIH) to inquire about pursuing the government's claim to patent rights to the AIDS drug AZT. As a result of those discussions, Barr Laboratories received a non-exclusive license from NIH to manufacture and market a generic AZT on July 11, 1991. The agreement between Barr and NIH obligates the company to pursue the NIH claim in federal court at its own expense.

The attached article by Brian Wolfman from the January/February issue of Public Citizen details the NIH claim to at least the status of co-inventor of AZT as well as the sordid history of the Burroughs Wellcome patent on AZT, an AIDS drug which was discovered and developed with taxpayer monies by NIH. These facts form the basis of the patent suit currently pending in the U.S. District Court for the Eastern District of North Carolina between Barr Laboratories and Burroughs Wellcome over the latter firm's claim the exclusive rights to AZT.

When Barr is allowed to market a generic version of AZT, NIH will receive a royalty which will be only partially offset by the legal cost to Barr. These legal costs exceed $2 million to date, and will cost at least $1.5 million more to take the case to trial. That trial is currently scheduled for June of this year.

Under the Waxman-Hatch Act, should Barr be successful in overturning the Burroughs' patent, the company would be entitled to six months of exclusivity after which time all other generic drug firms would be able to market their versions of AZT subject to FDA approval and license from NIH.

During the negotiations leading to the agreement with NIH, Barr offered to specify a price they would charge for AZT during the period of exclusivity in the contract. Apparently for ideological reasons, NIH declined the offer. Nonetheless, Barr has promised that it will sell the drug at approximately 50% of the Burroughs price unless that price failed to cover Barr's cost. The agreement between Barr and NIH is obviously in the public interest for at least two reasons.

First, Barr's entry into the market would dramatically reduce the price of AZT to persons infected with the HIV virus. Second, it would substantially reduce the price for AZT paid by the government. The direct and indirect payments, to date, from the Federal Treasury to Burroughs for AZT approach or exceed $500 million.

Thus far, the Department of Justice has provided some degree of cooperation to Barr in this matter. However, they have declined to intervene as a party in the case on behalf of NIH. Because of a quirk in the law, Barr was required to notify Burroughs of its intent to manufacture a generic version of AZT leaving Burroughs with the responsibility of bringing the lawsuit hence choosing the venue. Trying a case involving a firm as large as Burroughs Wellcome in its own backyard is a difficult matter. It would be very helpful for the U.S. Department of Justice to actively intervene on behalf of NIH.

Given the overriding public interest, not to mention the fiscal consequences to the taxpayers that financed the research and the simple justice involved for the NIH researchers, it would appear logical that the Justice Department would be enthusiastic about supporting Barr in court. To date, they have not agreed to this course of action.

Barr hopes that the Clinton Administration, with its commitment to control of spiraling drug prices, fiscal responsibility, and an expanded effort to help the victims of this terrible plague, will view the public interest in this lawsuit a good bit differently than their predecessors. Hopefully, hearings like this will also help prompt positive action instead of empty excuses.

Sleight-of-Hand with AZT Patent Is Costly to AIDS Patients

AZT Should Be Public Property

by Brian Wolfman

On July 3, 1985, U.S. government scientists, under the direction of Dr. Samuel Broder of the National Cancer Institute, were the first to administer the drug AZT to an AIDS patient, at one of the institute's clinics in Bethesda, MD. Within weeks, Broder (now the Institute's director) and his colleagues concluded that AZT indeed slowed the growth of the deadly virus and, thus, presented the potential to improve and prolong the lives of people with AIDS.

AZT is still only one of two drugs approved for use in slowing the insidious AIDS virus, which has killed more than 150,000 Americans and now infects more than 10 million people worldwide. Research for AZT cost more than $2 million which was funded by taxpayers, but the medication has become an enormous cash source for a private pharmaceutical company.

How did it come to pass that AZT, after government scientists developed the medication for use against the AIDS virus, was placed in private hands under an exclusive patent granted to the Burroughs Wellcome Company? This is the key question raised in a lawsuit Public Citizen filed in March, 1991, in U.S. District Court in Washington, DC, on behalf of AZT users.

The issue arose because of the following history. In 1964, Dr. Jerome Horowitz of the Michigan Cancer Institute, operating under a National Cancer Institute grant, first synthesized AZT as an anti-cancer agent. When it proved unsuccessful as a treatment, AZT was shelved and the compound formula entered the public domain.

Twenty years later, government scientists discovered that a retrovirus, later named Human Immunodeficiency virus, or HIV, caused AIDS (Acquired Immune Deficiency Syndrome). The National Cancer Institute, with its experience in antiviral research, developed a lab almost overnight to test various compounds that it hoped might work against HIV. Scientists there were willing to risk working with samples of the deadly AIDS virus to try to combat it.

The Institute asked private companies to contribute chemicals that might be promising because of their known antiviral properties. Officials of Burroughs Wellcome initially refused, indicating they thought a drug for HIV infection did not present a profit potential. But the company finally relented and sent samples of the types of drugs, including AZT, that Broder of the Institute wanted. In early 1985, the Institute's lab—using unique tests it had developed—discovered that AZT inhibited HIV in the test tube, leading to the first patient experiment.

Under the Institute's direction, AZT was tested in more patients. In 1987, the Food and Drug Administration approved AZT for use by AIDS patients. AZT is not a perfect drug for slowing the HIV virus, but it's one of the two best we have now. (The other drug is called DDI. After learning a lesson in losing its rights to the AZT, the federal government retained the patent for DDI and granted a license to a private firm for the right to manufacture and sell it.)

This magnificent work of government scientists also was the beginning of a monumental rip-off. In 1986, just before the National Cancer Institute's work was to be published in the prestigious *Proceedings of the National Academy of Sciences* journal, officials of Burroughs Wellcome, located in the Research Triangle near Raleigh, NC, went to the U.S. Patent Office in Washington, DC, to stake out a 17-year claim on the use of AZT against HIV.

Burroughs Wellcome Company officials said that it alone had invented the process by which AZT could be used to fight HIV. In early 1988, the U.S. Patent Office, whose proceedings are conducted in secret, granted Burroughs Wellcome the exclusive patent for AZT.

What had Burroughs Wellcome actually done prior to the patent application? It sent the National Cancer Institute, as requested, lab samples of many compounds. That's all. Burroughs scientists never worked with live HIV in the test tube or in human patients. The company's scientists, according to Broder, admitted to him that they were afraid to work with the lethal virus.

And what did Burroughs Wellcome do after it received government approval to market the drug and while the patent application was pending? It made AZT the most expensive drug in history—costing more than $10,000 for each patient annually and imposing a crushing burden on people with AIDS. Moreover, this $10,000 cost was paid for by federally funded health-care programs, which many people with AIDS relied upon.

Because of enormous pressure from the AIDS community, and because the government-approved dosage has been cut in half, the price of AZT has dropped to the range of $2,000 to $3,500 a year.

But the price, and the revenues of Burroughs Wellcome, remain outrageous. Peter Arno, health economist and co-author of *Against the Odds: The Story of AIDS Drug Development Politics & Profits*, contends that from 1987 to 1992 AZT generated $1.4 billion in revenue for Burroughs Wellcome. Arno, associate professor in the Department of Epidemiology and Social Medicine at Montefiore Medical Center and Albert Einstein College of Medicine in New York City, said that in 1992 alone AZT generated $388 million for the company.

With AZT now approved for use by many HIV-infected individuals who have no AIDS symptoms (perhaps the most medically promising, and potentially the largest treatment group), Burroughs's revenues on AZT alone are estimated at a monstrous $500 million annually.

On March 18, 1991, Public Citizen filed a suit, *People with AIDS Health Group v. Burroughs Wellcome Company*, on behalf of an AIDS health group and two HIV patients—William J. Ceyrolles and William L. Neithamer, both of Washington, DC—to invalidate the AZT patent. Invalidation would allow other firms to make or import AZT, thus lowering the price.

The suit named the U.S. government as a defendant, because of its ownership interests in the patent, in the hope that the government would take a position. Within days of the suit's filing, National Institute of Health Director Bernadine Healy issued a statement agreeing with Public Citizen. She stated that the National Cancer Institute scientists deserved to have their names listed as inventors on the patent. Although the government ultimately was dropped from Public Citizen's suit, the government agreed to license its rights to a generic drug firm—Barr Laboratories, Inc., of Pamona, NY. Barr then challenged Burroughs Wellcome's patent in another suit, *Burroughs Wellcome v. Barr*, and promised to charge a much lower price for AZT.

Ultimately, the United States District Court in Washington, DC, dismissed Public Citizen's suit; the judge said the generic firm's suit was adequate protection for the consumer's interests. While Public Citizen disagrees with that assessment, it is confident that Burroughs Wellcome's monopoly will be broken in a court of law. The *Burroughs Wellcome v. Barr* case likely will go to trial early this year.

We expect the court to find the patent is invalid because the publicly-funded National Cancer Institute (NCI), not Burroughs Wellcome scientists, are the true inventors of this therapy. Burroughs, meanwhile, has a monopoly on AZT. We know that if the company faced even a single competitor, the price probably would be cut in half immediately.

Broder and his colleagues, at great personal risk and with too little public support at the time, made a critical discovery that is being exploited for enormous private gain. These NCI scientists are heroes—no more so, of course, than people with HIV who, like the people who brought Public Citizen's lawsuit, are determined not to surrender control of this horrible disease. ●

Brian Wolfman is a staff attorney with Public Citizen's Litigation Group.

Dear Congressman Stark, April 11, 1993

As a young woman suffering with Gaucher's disease, I want to thank you with all of my heart for speaking out against the insidious greed of the Genzyme Corporation.

I too spoke before Congressman Ron Wyden's subcommittee on January 25th of this year and have given interviews with our local papers, Time Magazine, Money Magazine, The New York Times, ABC and CBS. My father is a pioneer in raising funds to find a treatment for Gaucher's disease and he testified before Senator Metzenbaum's committee in 1992.

I read Genzyme Corporation's response to your comments and I want you to know that they are not telling the press the truth about the profits they are making from individuals with Gaucher's disease and their insurance companies.

The National Gauchers Foundation newsletter stated last month, quoted directly from Genzyme Corporation, that only 500 patients are on Ceredase, not the 800 that Genzyme Corp. has told the media. We ought to have that figure so that we can determine their profit margin accurately.

Genzyme's own literature and the information that the doctors currently have, is that the cost for a person my size, 5' 8", 136 pounds, would be $350,000 per year. Although they are currently testing patients with lower dosages, the results have not shown that lower dosages actually work. We know several patients who had to cut their dosages because they are running out of money not because the lower dosages have proven efficacious.

We received a call from a young father this week who has two children with Gaucher's disease. He had to choose which child would receive treatment because he couldn't get it for both- and as it is- his child who is on Ceredase, will meet his health insurance cap in three years. The Genzyme Corp. coaxed him into signing one child up for treatment with the promise that 1) they would provide for the second child if the insurance would not and 2) they would set up a fund which would help him pay his escalating health insurance premiums. Genzyme Corp. has not followed through on either promise.

Genzyme Corp. is now placing ads in Jewish Newspapers (Gaucher's disease is primarily a Jewish genetic disease) across the country under the guise of concerned doctors and clinics wanting to help those who have Gaucher's disease. These ads are especially pernicious because 1) They do not mention that the ads as well as these testing centers are financed by Genzyme Corporation in order to sell more product and 2) not every Gaucher's patient needs enzyme replacement therapy (Ceredase). A person diagnosed with Gaucher's disease should have a doctor, who is not paid by Genzyme Corporation, determining what is best for the patient's health, not the physician's or the drug company's pocket book!

I am enclosing a copy of my testimony, The Time Magazine article, a letter I wrote to the FDA protesting the unfair marketing practices of Genzyme Corporation, and an ad paid for by the Genzyme Corporation printed in the New Haven Jewish Ledger.

I hope that you will continue the fight against the immoral and outrageous practices of the Genzyme Corporation. I will send a copy of this letter to my representatives from Colorado with the fervent hope that, those of you in Congress with the interests of American citizens at heart, will help us to fight and win this battle against the greed of the few in the drug industry.

Warm regards,

Karen Guth

Karen Guth
6591 E. Dakota Ave.
Denver, CO. 80224
303-337-4811

February 4, 1993

David Kessler, Commissioner
Office of Orphan Products Development
Room 8-73, HF-35
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20957

Dear Mr. Kessler:

I am writing to you with the hope that you and your office will investigate the unethical and possibly illegal marketing practices of the Genzyme Corporation for the orphan drug, Ceredase.

Ceredase is, at this time, the only available orphan drug on the market for the treatment of Gaucher's Disease, which is a life-threatening and debilitating hereditary enzyme deficiency.

Genzyme's marketing practices, I believe, are contrary to the guidelines which you have pledged to enforce. Genzyme employs a sales force which aggressively markets to patients every few months to try to convince us to take Ceredase. The drug would cost me $350,000 a year and my fear has been that my family's health insurance cap would be met in a few years and we would then be without health insurance.

Each time I explain my situation to a Genzyme corporation salesperson, they ensure me that if I send my insurance policy to them their "reimbursement specialists' and lawyers will make sure that my insurance company will pay for my treatment. Both Mr. William Pursely, the vice president of marketing for Genzyme, and Mr. Michael Epstein, the President of the National Gauchers Foundation called me, at my home, to urge me to send them a copy of my personal health insurance policy.

The National Gauchers Foundation has a registry of Gauchers patients which is supposed to be confidential; however, they gave that list to the Genzyme Corporation and Genzyme mailed their marketing magazine and video tape directly to patients.(The envelopes show that they were postmarked in Massachusetts, not in the Washington D.C. area where the Foundation is located.

This is an outrage! These marketing tactics are an invasion of my privacy. On January, 25,1993, I gave public testimony to this fact to the House Subcommittee on Regulation, Business Opportunities and Energy, chaired by representative Ron Wyden.

In addition, the literature and tape which Genzyme distrubutes to the public gives erroneous information about the actual cost of the drug. One patient on their tape says it only costs about $20 per treatment and other literature says it costs $20,000 to $60,000 per year after the first year.

David Kessler, Commisioner
February 4, 1992
page two

The Office of Technology Assessment's (OTA) report on Ceredase averages the cost at $380,000 per year, and it clearly says that there is no proof that lower doses will be effective. An NEJM article that was recently published describes a lower dose of Ceredase given more frequently (three times a week rather than once every two weeks). However, the study was done on a very small number of patients and it is very controversial. Other low dose studies which are presently under way do not appear to show efficacy.

I now implore the FDA to investigate these matters and to require Genzyme Corporation to: 1) not market directly to patients; 2) make their literature truthful about the dosage and costs of Ceredase; 3) not mail information to patients or telephone them unless patients request it.

I look forward to your reply.

Very truly yours,

Karen D. Guth
6591 E. Dakota Ave.
Denver, CO 80224
303-377-6753

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Gaucher Treatment Center

DR. BARBARA R. POBER, M.D.

(203) 737-2754

This center provides diagnostic and treatment services to people of all ages who suffer from Gaucher Disease

MIRACLE DRUG: ONLY $350,000 A YEAR

CEREDASE, A BREAKTHROUGH TREATMENT for the crippling and sometimes fatal genetic disorder called Gaucher's disease, is changing lives, even saving them—but not always making them better. For Jeanne Rogal, 29, of Harrisburg, Pennsylvania, Ceredase has reduced the pain from her crumbling bones, removed the lipid deposits choking her liver, and restored her energy so she can enjoy life again. But with it comes a crushing financial burden: Ceredase can cost up to $350,000 for a year's treatment.

Rogal has already exhausted one health-insurance policy and is whittling down a second. Although Medicaid pays part of the cost of the drug, the government dictates brutally austere terms: if Rogal accepts the payments, she isn't allowed to own major assets or have a bank account with more than $250 in it. "I finally have this great new life where I can do things," she says, "and I can't even save the money for a vacation."

Ceredase, and the Massachusetts company called Genzyme that makes it, illustrates how some drug companies have turned government research and regulations into Big Business. The Federal Government financed the discovery of the drug and then paid tax dollars so that entrepreneurs could learn how to manufacture it. Now it is paying as much as 20% of the nation's Ceredase bill through Medicare and Medicaid. And Ceredase isn't the only high-priced drug that has flowed from government laboratories. The new chemotherapeutic taxol, as well as almost half of all other cancer drugs, owes its existence to government scientists, as do nearly all AIDS drugs.

JAMES COOK FOR TIME

Karen Guth refused the expensive drug

The story of Ceredase starts with government-sponsored scientists who in 1965 found that Gaucher's disease resulted from the lack of an enzyme. Later another group of government scientists patented a method for harvesting that enzyme, and contracted with researchers at Tufts University to supply the enzyme in large enough quantities for research.

During the 1980s the Tufts researchers gradually spun away from the university and started the biotech firm Genzyme. By then the government had spent nearly $9 million—fully 20% of all measurable research-and-development costs, according to the Office of Technology Assessment—to aid in developing Ceredase. Genzyme disputes the figure and says the government provided only 14% of the drug's development costs. Still, when the company brought its drug to market, it set the price extraordinarily high, claiming that the process of harvesting the enzyme from human placental tissue is expensive, a claim challenged by a growing number of Gaucher's patients. "This is the worst illustration of corporate greed I've seen," says Abbey Meyers, executive director of the National Organization for Rare Disorders. Responding to Meyers, Genzyme's chairman of the board, Henri Termeer, says, "It's not a matter of greed. It's a high-cost product. There is no flexibility on price here."

Genzyme's marketing tactics have also raised eyebrows. Company salesmen use the unusual tactic of contacting Gaucher's victims and their doctors directly, enticing them with videos and publications suggesting that a healthy, pain-free life is at last at hand.

In spite of the aggressive commercial campaign, a mere 800 of the 11,000 Gaucher's patients who need treatment have signed up for Ceredase. One who refused, Denver teacher Karen Guth, estimates she would need to spend $350,000 for the drug each year. "It's a terrible position to put human beings in," she says. —*By Dick Thompson/ Washington*

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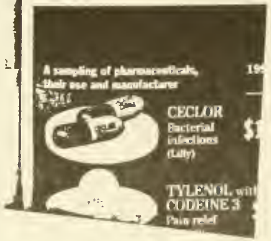
the first major target of health-care reformers' wrath. The President last month blasted the price of prescription drugs as "shocking" and blamed vaccinemakers for pursuing "profits at the expense of our children." His remarks came a day after Hillary Rodham Clinton denounced the cost of childhood vaccines—which have risen 1,000% in a decade—and suggested that drugmakers would oppose the Administration's forthcoming health-care reforms. The industry's earnings also came under attack; Democratic Congressman Henry Waxman of California last week unveiled a 354-page Office of Technology Assessment report that charged that drug firms raked in $2 billion of "excess profits" a year and lavished vast sums on campaigns to encourage doctors towards of $200 million just to get a product to market," says a spokesman for Johnson & Johnson. "And for every one that gets there, there are several that fail because of unfavorable side effects, no demonstrable increase in benefits, or a variety of other reasons." Moreover, experts say, costly marketing programs are a vital extension of the companies' research efforts. Declares Boston University economist Laurence Kotlikoff: "What good does it do to discover a health-improving drug and not have anyone know about it?"

FOR SMALLER COMPANIES, THE PRICE of failure can indeed be catastrophic. Shares of the biotech firm Synergen plummeted 68% in a single day last week after the company dis-

in Chicago, "the incentive to do research will diminish, and our competitive position in the world will decline."

But how much profit do drug firms really need? Thanks to sky-high pricing, as much as 16% of the industry's sales flow straight to the bottom line, or about three times the average for FORTUNE 500 companies. Fueling those profits, wholesale drug prices rose nearly six times as fast as inflation between 1980 and 1992, according to a recent report for the Senate Special Committee on Aging. Moreover, a single successful drug can deliver a bonanza. Merck's Mevacor, the first drug to lower cholesterol levels, arrived in 1987 and now rings up sales of $1 billion a year. And Merck's patent doesn't expire until 1999.

Prices can swell even more at the retail level as pharmacies and drugstore chain



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